The American Journal of Cardiology

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240 TOTAL

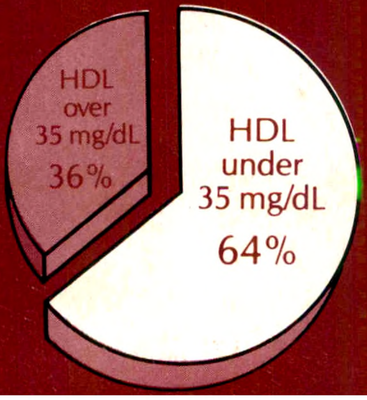
<35 HDL

mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS (PROCAM TRIAL)[2]



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Early Clinical Results of Long Coronary Arteriotomy, Endarterectomy and Reconstruction Combined with Multiple Bypass Grafting for Severe Coronary Artery Disease

Rolf G. Sommerhaug, Steven F. Wolfe, Daniel A. Reid, and David E. Lindsey

We performed long coronary arteriotomy, endarterectomy and reconstruction, and multiple bypass graft surgery over a 2.5-year period in 130 of 329 patients to ensure complete myocardial infarction. Data indicate that complete myocardial revascularization can be effectively accomplished by this approach in patients with severe coronary artery disease.

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Long-Term Results of Successful and Failed Angioplasty for Chronic Total Coronary Arterial Occlusion

Leo Finci, Bernhard Meier, Josiane Favre, Alberto Righetti, and Wilhelm Rutishauser

One hundred consecutive patients with total coronary occlusion underwent successful percutaneous transluminal coronary angioplasty and were followed for a mean period of 2 years. Results were compared with 100 consecutive patients in whom PTCA failed. Patients with successful coronary angioplasty of chronic total occlusion appeared to fare significantly better than those with failed angioplasty.

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Emergency Percutaneous Transluminal Coronary Angioplasty for Acute Myocardial Infarction in Patients 70 Years of Age and Older

Tommy C. Lee, Louise A. Laramee, Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Robert W. Ligon, and Geoffrey O. Hartzler

Direct percutaneous transluminal coronary angioplasty was performed to establish reperfusion during acute myocardial infarction in 105 elderly patients. Primary success was achieved in 91% of the infarct-related arteries. Direct PTCA is effective in salvaging ischemic myocardium during acute MI in the elderly patient and is associated with a high success rate and low complication rate.

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Circadian Distribution of the Characteristics of Ischemic Episodes in Patients with Stable Coronary Artery Disease

Dirk Hausmann, Peter Nikutta, Hans-Joachim Trappe, Werner G. Daniel, Paul Wenzlaff, and Paul R. Lichtlen

We studied circadian rhythms in 111 patients with coronary artery disease. There was significant variation (high values between 8 and 10 A.M. and between 4 and 5 P.M.). Heart rate at onset of ischemic episodes and maximal heart rate during ischemic episodes were lower between midnight and 6 A.M. than during other times of the day. Circadian rhythm in ischemic activity is based on a comparable variation in myocardial oxygen requirements.

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Long-Term Follow-Up of Postmyocardial Infarction Patients with Ventricular Tachycardia or Ventricular Fibrillation Treated with Amiodarone

Boris Strasberg, Jairo Kusniec, Bruria Zlotikamien, Aviv Mager, and Samuel Sclarovsky

Electrophysiologic studies revealed that low-dose amiodarone in 33 patients with ventricular tachycardia after healed myocardial infarction is an effective first-line antiarrhythmic therapy with a low incidence of adverse effects.

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Comparison of Nicorandil and Atenolol in Stable Angina Pectoris

Liam O. Hughes, Edward L. Rose, Avijit Lahiri, and Edward B. Raftery

We compared nicorandil (20 mg twice daily) with atenolol (100 mg once daily) in 37 patients with chronic stable angina pectoris. Both drugs produced significant and comparable improvements in predose exercise time.

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Effects of Nitroglycerin at Therapeutic Doses on Platelet Aggregation in Unstable Angina Pectoris and Acute Myocardial Infarction

Jean Diodati, Pierre Théroux, Jean-Gilles Latour, Lucie Lacoste, Jules Y.T. Lam, and David Waters

We evaluated platelet aggregation in 10 patients (5 with unstable angina, 5 with acute myocardial infarction) before, during and after a 45-minute infusion of nitroglycerin. Nitroglycerin decreased platelet aggregation to adenosine diphosphate or to thrombin in all patients by 50%. This inhibition was rapidly reversible after discontinuation of the drug.

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Significance of Dipyridamole-Induced Transient Dilation of the Left Ventricle During Thallium-201 Scintigraphy in Suspected Coronary Artery Disease

Pierre Chouraqui, Erwin A. Rodrigues, Daniel S. Berman, and Jamshid Maddahi

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We studied transient dilation of the left ventricle during dipyridamole stress-redistribution thallium-201 scintigraphy in 73 patients who underwent both dipyridamole thallium-201 study and coronary angiography. Patients with an abnormal transient dilation ratio (≥1.12) had a higher incidence of 3-vessel disease, higher prevalence of collaterals, more extensive myocardial reversible defects and a higher incidence of dipyridamole-induced anginal chest pain. LV transient dilation during dipyridamole thallium-201 scintigraphy is a marker of extensive myocardial ischemia.

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Coronary Sinus Lysophosphatidylcholine Accumulation During Rapid Atrial Pacing

Steven P. Sedlis, Jeffrey M. Sequeira, and Henry M. Altszuler

We measured coronary sinus lysophosphatidylcholine during pacing stress. Coronary sinus LPC concentration increased from 69.1 ± 5.3 μM at baseline to 101.7 ± 9.0 μM at 4 minutes and to 178.0 ± 18.0 μM at peak pacing in 14 ischemic patients ($p < 0.01$). In contrast, coronary sinus LPC did not increase significantly in 6 nonischemic patients and LPC did not increase in mixed venous or arterial blood from ischemic patients: thus, coronary sinus LPC accumulation may be an early marker of ischemia in humans.

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Clinical and Pathophysiologic Correlates of ST-T-Wave Abnormalities in Patients with Coronary Artery Disease

David M. Mirvis, Faten El-Zeky, Roger Vander Zwaag, Kodangudi B. Ramanathan, James H. Crenshaw, Frank H. Kroetz, and Jay M. Sullivan

We evaluated clinical, hemodynamic and coronary angiographic data from 9,801 patients to determine the correlates of ST-segment depression on the routine electrocardiogram. The most significant correlates of ST-T wave abnormalities were presence of left ventricular contraction abnormality, followed by age, gender, left anterior descending coronary artery disease, elevated end-systolic volume index and hypertension.

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Changes in Diameter of Coronary Narrowings and Translesional Hemodynamics After Intracoronary Nitroglycerin

Brian P. Kimball, Sanh Bui, and Nick Dafopoulos

The effect of intracoronary nitroglycerin on coronary stenosis dimensions and translesional hemodynamics (pressure gradients) was evaluated using quantitative coronary arteriography and standard Newtonian fluid dynamic equations. At baseline flow velocity, intracoronary nitroglycerin predicted a decrease in average transstenotic pressure gradient, although accelerated flow velocities may actually increase hemodynamic obstruction, particularly in severe stenoses. The potential for transmyocardial flow maldistribution and subendocardial ischemia exists after intracoronary nitroglycerin.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Cycle-Length Response of Ventricular Tachycardia Associated with Coronary Artery Disease to Procainamide and Amiodarone

Paul T. Vaitkus, Alfred E. Buxton, Mark E. Josephson, and Francis E. Marchlinski

Forty patients with inducible, sustained, monomorphic ventricular tachycardia at a drug-free baseline electrophysiologic study after procainamide infusion and during oral amiodarone therapy were examined to determine if the cycle-length response of the VT was similar to both agents. We found a significant correlation between VT cycle length and percent change in cycle length from baseline for the 2 agents. However, only 60% of the patients had cycle lengths on the 2 agents that differed by <10%; fewer than 20% of patients had additional slowing on amiodarone as compared to procainamide.

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Atrial Endocardial Mapping in the Rare Form of Atrial Flutter

Francisco G. Cosio, Antonio Goicolea, Maria López-Gil, Fernando Arribas, José Luis Barroso, and Ramiro Chicote

Endocardial mapping of the rare and common form of atrial flutter revealed that most cases of rare AF are due to right atrial macroreentry with clockwise rotation of activation, but that counterclockwise circuits can also produce rare AF patterns.

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Clinical, Echocardiographic and Doppler Correlates of Clinical Instability with Onset of Atrial Fibrillation

Marc D. Tischler, Thomas H. Lee, Kim A. McAndrew, Paul E. Sax, Martin St. John Sutton, and Richard T. Lee

Eighty-seven consecutive patients with new-onset atrial fibrillation who had echocardiograms recorded during that admission while in sinus rhythm were studied to identify clinical and Doppler echocardiographic correlates of instability with AF onset. Multiple logistic regression analysis identified 3 variables as independent predictors of clinical instability with AF onset. Data revealed that patients who are more dependent on the atrial contribution to ventricular filling are at increased risk of instability with AF due to the loss of atrial systole.

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Day-to-Day Reproducibility of Antiarrhythmic Drug Trials Using Programmed Extrastimulus Techniques for Ventricular Tachyarrhythmias Associated with Coronary Artery Disease

Peter J. Kudenchuk, Jack Kron, Charles G. Walance, Joel E. Cutler, Karen K. Griffith, and John H. McAnulty

Forty-nine patients with coronary artery disease and documented clinical sustained ventricular tachycardia or fibrillation were tested twice during treatment with an identical antiarrhythmic medication at similar therapeutic plasma concentrations using an identical programmed electrical stimulation protocol.Tested drugs included procainamide, quinidine, disopyramide and phenytoin. Our data indicate that drug trials directed by programmed stimulation should be cautiously interpreted because time-associated changes can mimic a change attributed to a beneficial or deleterious drug effect.

SYSTEMIC HYPERTENSION

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Exaggerated Pressure Response to Exercise in Men at Risk for Systemic Hypertension

Michael F. Wilson, Bong Hee Sung, Gwendolyn A. Pincomb, and William R. Lovallo

Cardiovascular responses to exercise in normotensive men were compared between those at high risk and those at low risk of hypertension. During moderate exercise, 35% of the high-risk men had exaggerated blood pressure responses versus 0% of low-risk men. Cardiac output was the same at rest and in response to exercise, whereas peripheral resistance during exercise had less decline in high-risk exaggerated responders.

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Factors Influencing Progression of Mitral Regurgitation After Transarterial Balloon Valvuloplasty for Mitral Stenosis

Manuel Sancho, Alfonso Medina, José Suárez de Lezo, Enrique Hernandez, Manuel Pan, Ignacio Coello, Miguel Romero, Francisco Melián, José Segura, Francisco Jiménez, Ricardo Vivancos, Eva Laraudogoitia, and Federico Vallés

We analyzed factors affecting progression of mitral regurgitation after transarterial mitral balloon valvuloplasty in 200 patients. Multivariate analysis selected age, left ventricular volumes and ejection fraction as independent predictors of MR progression. All these factors suggest that MR progression after balloon valvuloplasty could be related to a more advanced degree of disease.

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Diagnostic Accuracy of Right Ventriculography in Arrhythmogenic Right Ventricular Cardiomyopathy

Luciano Daliento, Giulio Rizzoli, Gaetano Thiene, Andrea Nava, Marco Rinuncini, Raffaello Chioin, and Sergio Dalla Volta

Diagnostic sensitivity and specificity of right and left cineventriculogram parameters were evaluated by multivariate logistic analysis in 32 patients with arrhythmogenic right ventricular cardiomyopathy, 27 with biventricular dilated cardiomyopathy, 28 with atrial septal defect and 18 normal subjects. Our data indicate that arrhythmogenic RV cardiomyopathy presents quantitative volumetric and hemodynamic as well as qualitative features that clearly distinguish it from dilated cardiomyopathy and confirm its nosographic autonomy among the primary diseases of the myocardium.

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Effect of Preload Change on Resting and Exercise Cardiac Performance in Hypertrophic Cardiomyopathy

Wan L. Chan, David M. Gilligan, Eng L. Ang, and Celia M. Oakley

Rest and exercise hemodynamic function after diuretic was compared to that after fluid loading in 13 patients with hypertrophic cardiomyopathy. Although ventricular filling pressures were significantly increased with volume load and decreased with diuretic, exercise cardiac index, stroke index and exercise capacity were unchanged. Our data suggest that these patients are operating on the plateau of the Frank-Starling (filling pressure/output) curve and that diuretics can be used safely in selected patients with hypertrophic cardiomyopathy.

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Sanjeev Saksena and Isaac Gielchinsky

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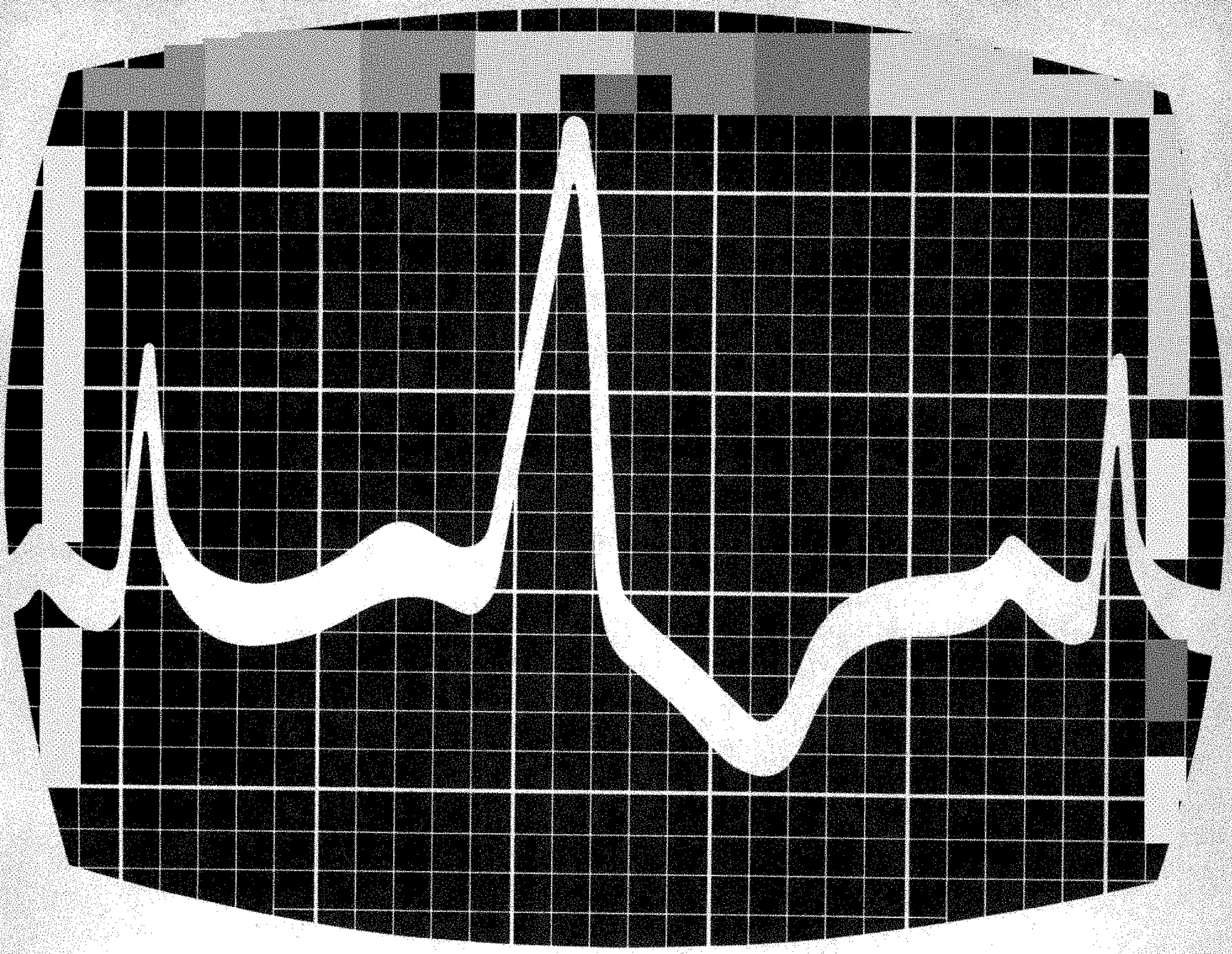

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CORONARY ARTERY DISEASE

651

Early Clinical Results of Long Coronary Arteriotomy, Endarterectomy and Reconstruction Combined with Multiple Bypass Grafting for Severe Coronary Artery Disease

Rolf G. Sommerhaug, Steven F. Wolfe, Daniel A. Reid, and David E. Lindsey

Over a 2.5-year period, we performed long coronary arteriotomy, endarterectomy and reconstruction (principally left anterior descending artery), and multiple bypass graft surgery (mean graft rate 9) in 130 of 329 (40%) diffusely diseased patients to ensure complete myocardial revascularization. The operative mortality was 2.3% and the perioperative infarction was 1.5%. Patency rates in randomly selected patients were 99% for conduits, 98% for anastomoses and 97% for conduits to endarterectomized and reconstructed arteries. Postoperatively at 20 months, 120 of the 121 patients (99%) were in angina class I by Canadian Cardiovascular Society classification, and 63 of 71 patients (89%) had a normal treadmill exercise stress test. Thus, early clinical results indicate that complete myocardial revascularization by this aggressive surgical approach is effective in patients with severe coronary artery disease.

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Long-Term Results of Successful and Failed Angioplasty for Chronic Total Coronary Arterial Occlusion

Leo Finci, Bernhard Meier, Josiane Favre, Alberto Righetti, and Wilhelm Rutishauser

The results after a mean period of 2 years of successful percutaneous transluminal coronary angioplasty (PTCA) in 100 consecutive patients with chronic total coronary occlusion were compared with those in 100 consecutive patients whose PTCA was unsuccessful. In the group with successful PTCA, there were significantly more symptom-free patients (57 vs 26), less patients with bypass surgery (7 vs 37), and results of stress testing were better.

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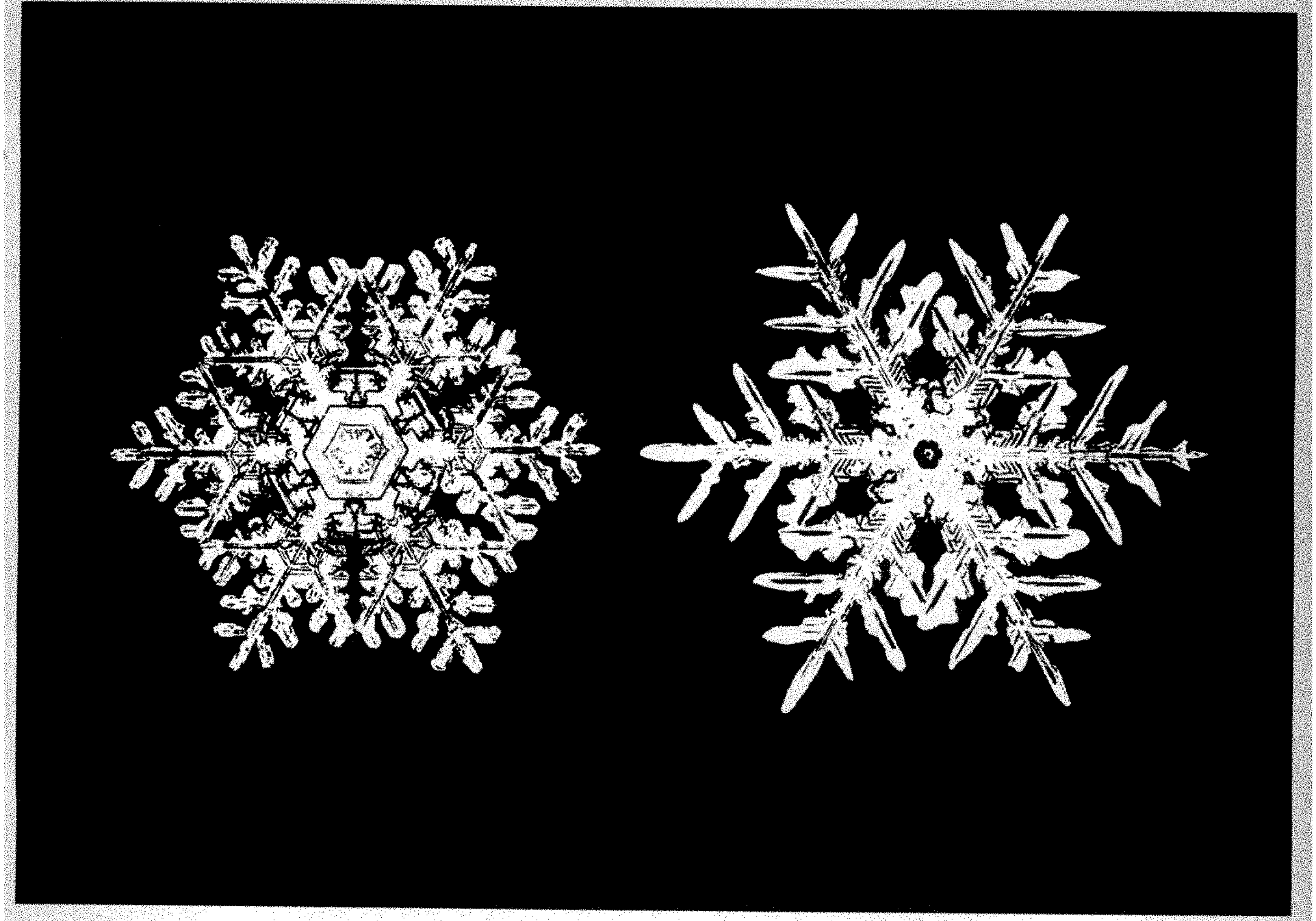

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Pharmaceutical Manufacturers Association

IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

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Emergency Percutaneous Transluminal Coronary Angioplasty for Acute Myocardial Infarction in Patients 70 Years of Age and Older

Tommy C. Lee, Louise A. Laramee, Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Robert W. Ligon, and Geoffrey O. Hartzler

Direct angioplasty was performed as the primary means of establishing reperfusion during acute myocardial infarction in 105 elderly patients (mean age 75 ± 4 years) at a mean of 5.5 ± 4.0 hours from symptom onset. Primary success was achieved in 91% of the infarct-related arteries. Global ejection fraction improved from 54 ± 13% to 61 ± 15% ($p < 0.001$). The overall in-hospital mortality was 18%. No cerebral or gastrointestinal hemorrhage occurred in this series. Direct angioplasty, when applied by experienced operators in a facility geared toward its application as primary therapy, is an effective and safe method to salvage myocardium and improve mortality in this high-risk group.

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Circadian Distribution of the Characteristics of Ischemic Episodes in Patients with Stable Coronary Artery Disease

Dirk Hausmann, Peter Nikutta, Hans-Joachim Trappe, Werner G. Daniel, Paul Wenzlaff, and Paul R. Lichtlen

One hundred eleven patients with stable angina pectoris, positive exercise test results and angiographically proven coronary artery disease were studied. Ambulatory electrocardiographic monitoring revealed 101 symptomatic and 298 asymptomatic ischemic episodes. Number of ischemic episodes and cumulative duration of ischemia showed a significant circadian variation, with the highest values between 8 and 10 A.M. and between 4 and 5 P.M., associated with a similiar circadian variation of heart rate. Mean duration of ischemic episodes, maximal amplitude of ST-segment depression and increase in heart rate before onset of ischemic episodes showed no significant circadian variation. Heart rate at the onset of ischemic episodes and maximal heart rate during ischemic episodes were lower between midnight and 6 A.M. than during other hours of the day. It is concluded that the circadian rhythm in ischemic activity is predominantly based on a comparable variation in myocardial oxygen requirements.

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Long-Term Follow-Up of Postmyocardial Infarction Patients with Ventricular Tachycardia or Ventricular Fibrillation Treated with Amiodarone

Boris Strasberg, Jairo Kusniec, Bruria Zlotikamien, Aviv Mager, and Samuel Sclarovsky

Thirty-three patients with ventricular tachycardia (VT) or fibrillation (VF) secondary to a healed myocardial infarction were treated with low-dose amiodarone. Mean age was 69 ± 9 years and mean left ventricular ejection fraction 29 ± 8%. Thirty of the patients were men. Predischarge

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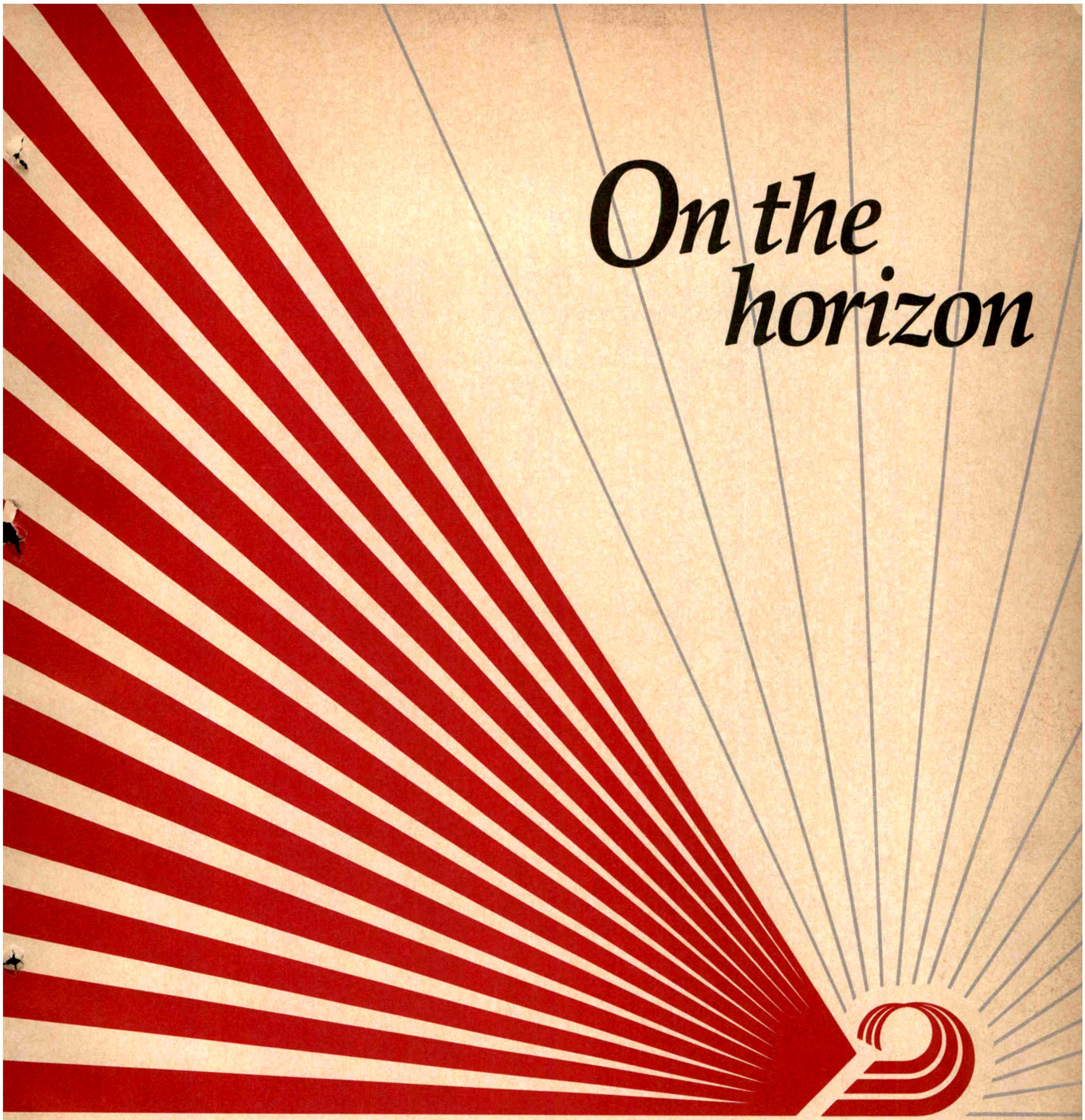

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electrophysiologic study revealed inducible sustained VT in 8 and either nonsustained VT or noninducible VT in 25 patients. After a mean follow-up of 27 ± 7 months, 11 patients (33%) died, 5 suddenly and 6 from nonarrhythmic causes. Five patients had nonfatal recurrences of VT. Toxicity was uncommon and there was no need to discontinue the medication.

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Comparison of Nicorandil and Atenolol in Stable Angina Pectoris

Liam O. Hughes, Edward L. Rose, Avijit Lahiri, and Edward B. Raftery

The efficacy of nicorandil (20 mg twice daily) was compared with atenolol (100 mg once daily) in 37 patients with chronic stable angina using a randomized, placebo-controlled, parallel study design. Treadmill exercise tests were performed at the end of each treatment phase immediately before and 2 hours after the morning dose of medication. After 6 weeks of therapy, nicorandil and atenolol produced significant and comparable improvements in predose exercise time: +1.47 (0.40) minutes with nicorandil ($p < 0.005$) and +1.33 (0.29) minutes with atenolol ($p < 0.001$). Whereas the predose peak exercise double product was reduced with atenolol (−43.6 units; $p < 0.001$), an increase (+7.56 units; difference not significant) was noted with nicorandil. Nicorandil and atenolol produce comparable improvement in exercise time in patients with stable angina. This new agent may be beneficial in patients with angina in whom β blockers are contraindicated, although headaches may be unacceptable in some patients.

683

Effects of Nitroglycerin at Therapeutic Doses on Platelet Aggregation in Unstable Angina Pectoris and Acute Myocardial Infarction

Jean Diodati, Pierre Théroux, Jean-Gilles Latour, Lucie Lacoste, Jules Y.T. Lam, and David Waters

Platelet aggregation was evaluated in 10 patients (5 with unstable angina, 5 with acute myocardial infarction) before, during and after a 45-minute infusion of nitroglycerin. The tests were performed at bedside on whole blood using an impedance aggregometer. Nitroglycerin decreased platelet aggregation to adenosine diphosphate or to thrombin in all patients by ≥50%. This inhibition was rapidly reversible after discontinuation of the drug.

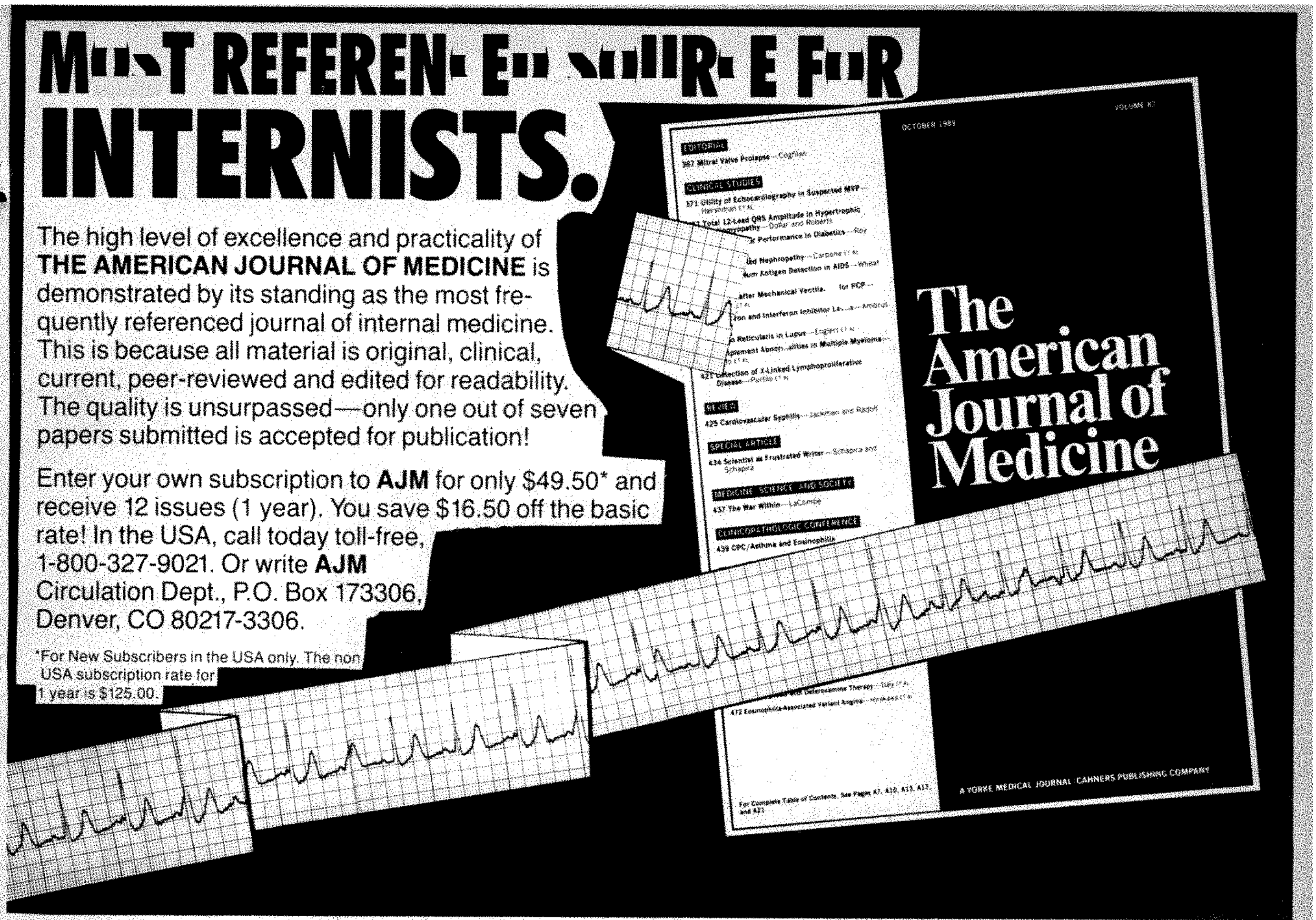
689

Significance of Dipyridamole-Induced Transient Dilation of the Left Ventricle During Thallium-201 Scintigraphy in Suspected Coronary Artery Disease

Pierre Chouraqui, Erwin A. Rodrigues, Daniel S. Berman, and Jamshid Maddahi

The occurrence and significance of transient dilation of the left ventricle during dipyridamole stress-redistribution thallium-201 scintigraphy was studied in 73 patients who underwent both dipyridamole thallium-201

Continued on page A24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study and coronary angiography. In the 11 patients with normal coronary arteriograms or <50% coronary stenosis, the transient dilation ratio was 0.98 ± 0.046. An abnormal transient dilation ratio, defined as ≥1.12, was present in 15 patients who were compared with 58 with a normal ratio. Considering clinical, scintigraphic and angiographic variables, the former group had a significantly higher incidence of 3 critical (≥90%) coronary stenoses (33 vs 5%), higher prevalence of collaterals (67 vs 24%), more extensive myocardial reversible defects by planar (71 vs 10%) or by single-photon emission computed tomography imaging (87.5 vs 35%) and a higher incidence of dipyridamole-induced anginal chest pain (53 vs 22%). An abnormal transient dilation ratio was a specific marker of multivessel (87%) or 3-vessel (85%) critical coronary disease. Thus, left ventricular transient dilation observed during dipyridamole thallium-201 scintigraphy is a marker of extensive myocardial ischemia caused by underlying extensive critical coronary stenoses.

695

Coronary Sinus Lysophosphatidylcholine Accumulation During Rapid Atrial Pacing

Steven P. Sedlis, Jeffrey M. Sequeira, and Henry M. Altszuler

We measured coronary sinus lysophosphatidylcholine (LPC) during pacing stress. Coronary sinus LPC concentration increased from 69.1 ± 5.3 μM at baseline to 101.7 ± 9.0 μM at 4 minutes and to 178.0 ± 18.0 μM at peak pacing in 14 ischemic patients ($p < 0.01$). In contrast, coronary sinus LPC did not increase significantly in 6 nonischemic patients and LPC did not increase in mixed venous or arterial blood from ischemic patients: thus, coronary sinus LPC accumulation may be an early marker of ischemia in humans.

699

Clinical and Pathophysiologic Correlates of ST-T-Wave Abnormalities in Patients with Coronary Artery Disease

David M. Mirvis, Faten El-Zeky, Roger Vander Zwaag, Kodangudi B. Ramanathan, James H. Crenshaw, Frank H. Kroetz, and Jay M. Sullivan

Clinical, hemodynamic and coronary angiographic data from 9,801 patients were evaluated to determine the correlates of ST-segment depression on the routine electrocardiogram. ST depression was more prevalent in older male and nonwhite patients with hypertension or diabetes and who smoked cigarettes. Pathophysiologic variables associated with the ST-T abnormality included severe coronary disease, especially involving the left anterior descending artery, and left ventricular contraction abnormalities.

705

Changes in Diameter of Coronary Narrowings and Translesional Hemodynamics After Intracoronary Nitroglycerin

Brian P. Kimball, Sanh Bui, and Nick Dafopoulos

The effect of intracoronary nitroglycerin on coronary stenosis dimensions and translesional hemodynamics (pressure gradients) was evaluated using quantitative coronary arteriography and standard Newtonian fluid dy-

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namic equations. Transstenotic pressure gradients were estimated at both baseline and increased flow velocities, because "high-dose" intracoronary nitroglycerin (200 μg) can produce transient myocardial hyperemia. Average minimum stenotic diameter increased, while relative percent diameter stenosis decreased after nitroglycerin, with the greatest changes in the least severe narrowings. At baseline flow velocity, intracoronary nitroglycerin predicted a decrease in average transstenotic pressure gradient, although accelerated flow velocities may actually increase hemodynamic obstruction, particularly in severe stenoses. The potential for transmyocardial flow maldistribution and subendocardial ischemia exists after intracoronary nitroglycerin.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

710

Cycle-Length Response of Ventricular Tachycardia Associated with Coronary Artery Disease to Procainamide and Amiodarone

Paul T. Vaitkus, Alfred E. Buxton, Mark E. Josephson, and
Francis E. Marchlinski

Forty patients with inducible, sustained, monomorphic ventricular tachycardia (VT) at a drug-free baseline electrophysiologic study, after procainamide infusion and during oral amiodarone therapy, were examined to determine if the cycle-length response of the VT was similar for both agents. We found a significant correlation between VT cycle length and percent change in cycle length from baseline for the 2 agents. However, only 60% of the patients had cycle lengths on the 2 agents that differed by <10%. Fewer than 20% of patients exhibited additional slowing on amiodarone as compared to procainamide.

715

Atrial Endocardial Mapping in the Rare Form of Atrial Flutter

Francisco G. Cosio, Antonio Goicolea, María López-Gil, Fernando Arribas,
José Luis Barroso, and Ramiro Chicote

Sequential endocardial right atrial mapping in 7 cases of "rare" atrial flutter (AF), inscribing positive deflections in lead II, revealed 2 types of circular activation. In 5 cases septal and posterior wall activation was craniocaudal and anterior and lateral wall activation was caudocranial (clockwise circuit). In 2 cases activation was identical to that typically recorded in common AF: craniocaudal in the anterior and lateral walls and caudocranial in the septal and posterior walls (counterclockwise). Left atrial activation seemed to play a passive role. The area closing the circuit was localized in the right atrial floor, between the inferior vena cava and the tricuspid ring. An area of block was present between the lateral and posterior walls. Rotation sense does not explain the surface electrocardiographic pattern by itself, but most cases of rare flutter, with positive deflections in lead II, are associated with right atrial macroreentry, with a rotation sense opposite to that found in typical common flutter.

Continued on page A30

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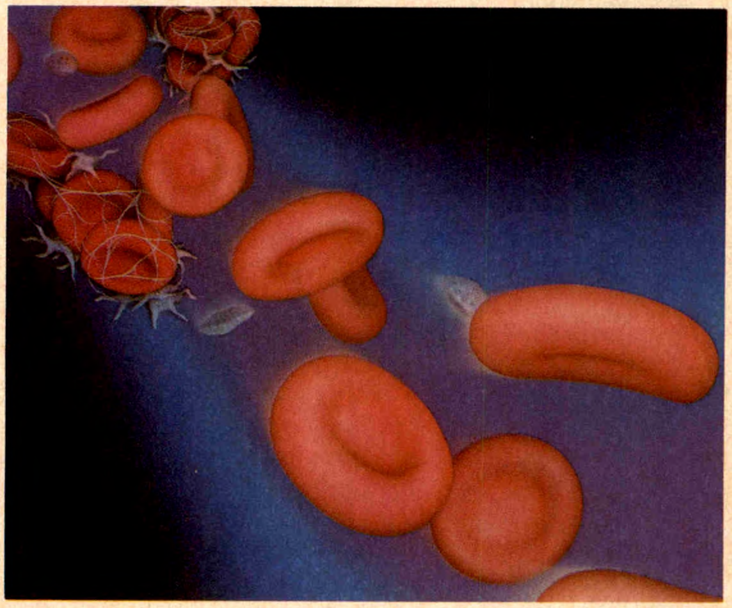

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2. Demke DM, Luderer JR, Wakefield KL, et al: The effect of itazigrel and aspirin on the mucosa of the esophagus, stomach, and duodenum of normal subjects. *J Clin Pharmacol* 1987; 27: 916-920.
3. Data on file, SmithKline Consumer Products, a SmithKline Beckman Company.

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721

Clinical, Echocardiographic and Doppler Correlates of Clinical Instability with Onset of Atrial Fibrillation

Marc D. Tischler, Thomas H. Lee, Kim A. McAndrew, Paul E. Sax,
Martin St. John Sutton, and Richard T. Lee

To identify predictors of which patients are most likely to become unstable with the onset of atrial fibrillation (AF), we studied 87 consecutive patients with new-onset AF who had Doppler echocardiograms recorded during that admission while in sinus rhythm. Reviewers classified 51 (59%) as unstable because of the development of angina, congestive heart failure, hypotension or syncope. Doppler data on transmitral flow were analyzed by a single reviewer blinded to other clinical data. Multiple logistic regression analysis identified 3 variables as independent predictors of clinical instability with the onset of AF: (1) history of prior myocardial infarction ($p < 0.02$); (2) echocardiographic evidence of left ventricular dysfunction ($p < 0.03$); and (3) Doppler evidence of increased atrial filling fraction ($p < 0.0001$). The Doppler-derived atrial filling fraction is a powerful correlate of clinical response to new-onset AF.

725

Day-to-Day Reproducibility of Antiarrhythmic Drug Trials Using Programmed Extrastimulus Techniques for Ventricular Tachyarrhythmias Associated with Coronary Artery Disease

Peter J. Kudenchuk, Jack Kron, Charles G. Walance, Joel E. Cutler,
Karen K. Griffith, and John H. McAnulty

Forty-nine patients with coronary artery disease and documented clinical sustained ventricular tachycardia or fibrillation were tested twice during treatment with an identical antiarrhythmic medication at similar therapeutic plasma concentrations using an identical programmed electrical stimulation protocol. Sustained ventricular tachyarrhythmias were induced in 71% of patients during drug testing. Overall, induced arrhythmias were not reproducible in 22% of patients, irrespective of testing at even nearly identical therapeutic concentrations of identical antiarrhythmic medications. This variability could not be attributed to the electrophysiologic characteristics of the patients studied. Time-associated changes can mimic a change attributed to a beneficial or deleterious drug effect during programmed stimulation.

SYSTEMIC HYPERTENSION

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Exaggerated Pressure Response to Exercise in Men at Risk for Systemic Hypertension

Michael F. Wilson, Bong Hee Sung, Gwendolyn A. Pincomb, and
William R. Lovallo

Cardiovascular responses to exercise in normotensive men were compared between those at high risk (positive parental history of hypertension and high normal blood pressures) and low risk (negative history and low normal blood pressures) for future hypertension. During moderate exer-

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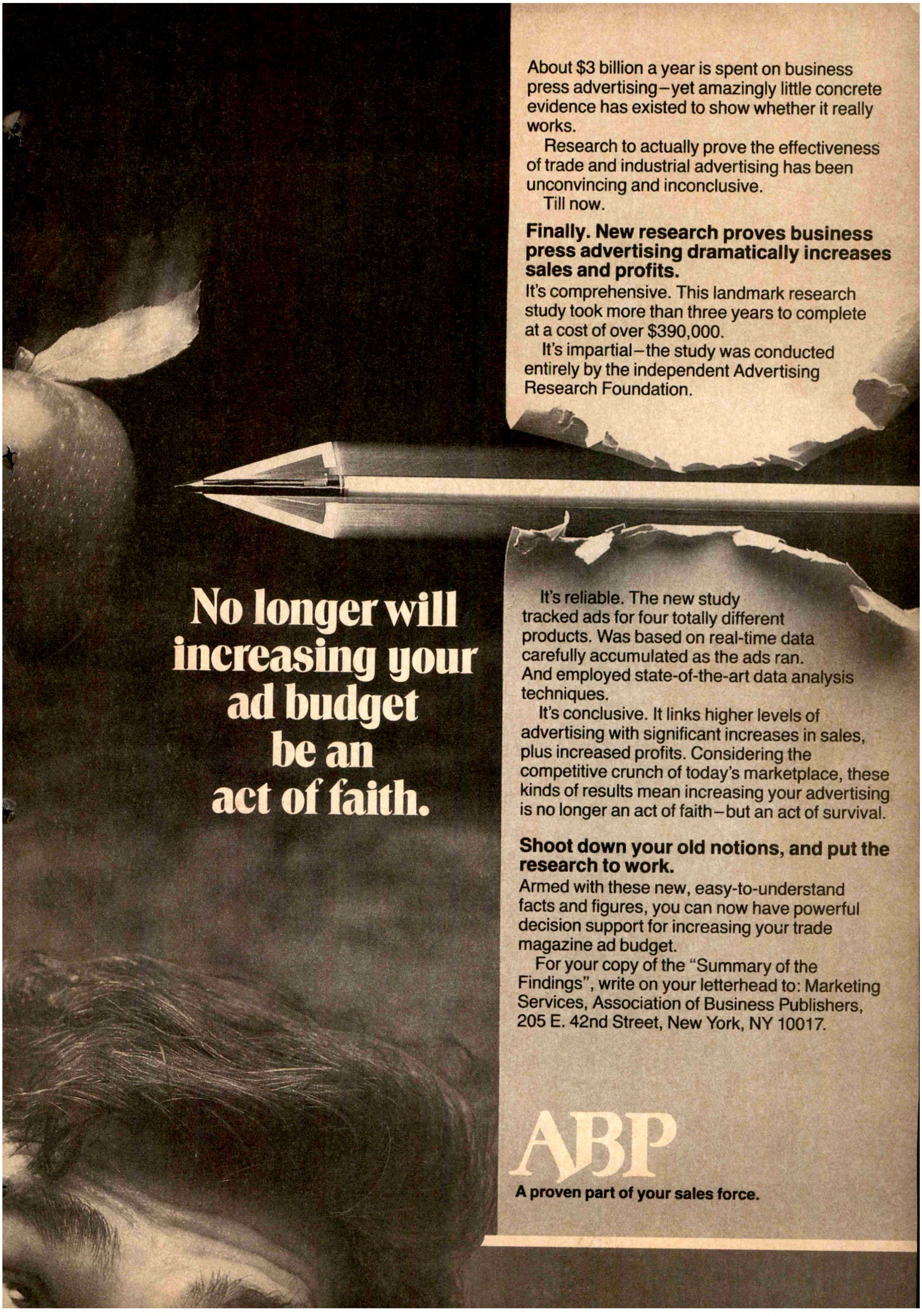
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cise, 35% of the high-risk men had exaggerated blood pressure responses ($\geq$230/100 mm Hg) versus 0% of low-risk men. Cardiac output was the same at rest and in response to exercise, whereas the high-risk exaggerated responders had less decline in peripheral resistance during exercise.

VALVULAR HEART DISEASE

737

Factors Influencing Progression of Mitral Regurgitation After Transarterial Balloon Valvuloplasty for Mitral Stenosis

Manuel Sancho, Alfonso Medina, José Suárez de Lezo, Enrique Hernandez, Manuel Pan, Ignacio Coello, Miguel Romero, Francisco Melián, José Segura, Francisco Jiménez, Ricardo Vivancos, Eva Laraudogoitia, and Federico Vallés

Factors affecting progression of mitral regurgitation (MR) after transarterial mitral balloon valvuloplasty in 200 patients were analyzed. Three patients had MR induced by a technical deficiency and they were excluded from analysis. Progression, defined as an increase to ≥ grade II in the angiographic degree of MR, was present in 30 patients (15%). Progression of MR was associated with an older age, chronic atrial fibrillation, larger left atrial size and left ventricular volumes, baseline mild MR, more severe stenosis and a lower ejection fraction. The multivariate analysis selected the age, the left ventricular volumes and the ejection fraction as independent predictors of progression of MR.

CARDIOMYOPATHY

741

Diagnostic Accuracy of Right Ventriculography in Arrhythmogenic Right Ventricular Cardiomyopathy

Luciano Daliento, Giulio Rizzoli, Gaetano Thiene, Andrea Nava, Marco Rinuncini, Raffaello Chioin, and Sergio Dalla Volta

Diagnostic sensitivity and specificity of right and left cineventriculogram parameters were evaluated by multivariate logistic analysis in 32 patients with arrhythmogenic right ventricular (RV) cardiomyopathy, 27 with biventricular dilated cardiomyopathy, 28 with atrial septal defect and 18 normal subjects. Analysis of variance of quantitative RV parameters showed that all values overlapped for the diagnosis of atrial septal defect and arrhythmogenic RV cardiomyopathy; overlapping extended to biventricular dilated cardiomyopathy for end-diastolic volume and infundibular dimensions. With regard to left ventricular parameters, a higher end-diastolic volume, and more severe impairment of the indexes of pumping and contractility significantly differentiated dilated cardiomyopathy from arrhythmogenic RV cardiomyopathy. The feature with the highest diagnostic probability of arrhythmogenic RV cardiomyopathy was transversally arranged hypertrophic trabeculae, separated by deep fissures; when this finding was associated with end-diastolic bulging of the infundibular anterior wall and subtricuspid area, the diagnostic sensitivity of cineangiography was 96% and specificity was 87%.

Continued on page A40

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746

Effect of Preload Change on Resting and Exercise Cardiac Performance in Hypertrophic Cardiomyopathy

Wan L. Chan, David M. Gilligan, Eng L. Ang, and Celia M. Oakley

Rest and exercise hemodynamic function after diuretic was compared to that after fluid loading in 13 patients with hypertrophic cardiomyopathy. Although ventricular filling pressures were significantly increased with volume load and decreased with diuretic, exercise cardiac index, stroke index and exercise capacity were unchanged. Our data suggest that these patients are operating on the plateau of the Frank-Starling (filling pressure/output) curve and that diuretics can be used safely in selected patients with hypertrophic cardiomyopathy.

BRIEF REPORTS

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Spontaneous Beat-to-Beat Variation of PR Interval in Normal Children

Richard L. Donnerstein, William A. Scott, and Thomas R. Lloyd

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Atrial Flutter in Patients Treated for Atrial Fibrillation with Propafenone

Challon J. Murdock, Alison E. Kyles, John A. Yeung-Lai-Wah, Anzhen Qi, Shirley Vorderbrugge, and Charles R. Kerr

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Transesophageal Echocardiography in the Evaluation of Prosthetic and Native Aortic Valves

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A Possible Mechanism for Neurologic Ischemic Events in Patients with Atrial Septal Aneurysm

Miguel Zabalgoitia-Reyes, Cesar Herrera, Dipeshkumar K. Gandhi, David J. Mehlman, David D. McPherson, and James V. Talano

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Effects of Left Ventricular Hypertrophy on the Signal-Averaged Electrocardiogram

Thomas C. Hilton, Terry Greenwalt, Chalapathirao V. Gudipati, Anthony C. Pearson, and Thomas A. Buckingham

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CASE REPORT

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Argon Laser Ablation or Modification of the Atrioventricular Conduction System in Refractory Supraventricular Tachycardia
Sanjeev Saksena and Isaac Gielchinsky

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CORONARY ARTERY DISEASE

The
American
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SEPTEMBER 15, 1990, VOL. 66, NO. 7

Early Clinical Results of Long Coronary Arteriotomy, Endarterectomy and Reconstruction Combined with Multiple Bypass Grafting for Severe Coronary Artery Disease

Rolf G. Sommerhaug, MD, Steven F. Wolfe, MD, Daniel A. Reid, MD,
and David E. Lindsey, MD

Within a 2.5-year period between 1985 and 1988, long coronary arteriotomy, endarterectomy and reconstruction (principally left anterior descending artery) and multiple bypass grafting (mean graft rate was 9) were performed in 130 of 329 patients (40%) with severe diffuse coronary artery disease to ensure complete myocardial revascularization. Ninety-two percent of the patients who underwent exercise testing had abnormal (>1 mm ST) depression and/or positive results on scintigraphy. Long coronary arteriotomy (5 to 12 cm), endarterectomy and reconstruction of the left anterior descending artery and its branches, were performed in 121 patients; of the left circumflex artery and its branches in 13 patients; and of the right coronary artery and its branches beyond the crux in 18 patients. Single endarterectomy and reconstruction was performed in 109 patients, double in 20 and triple in 1. The operative mortality was 2.3% and the perioperative infarction was 1.5%. Twenty-four patients (among them 38% who had undergone >1 previous bypass operation) were randomly selected and studied within 20 days after surgery. This group comprised a total of 69 coronary conduits of which 68 (99%) were patent, and a total of 206 coronary anastomoses of which 202 (98%) were patent. Thirty-two of 33 conduits (97%) to endarterectomized and reconstructed arteries were patent. One hundred and twenty-six of 127 patients were followed up for a mean of 20 months; 120 of the 121 patients (99%) were in angina class I by Canadian Cardiovascular Society classification, and 63 of 71 patients (89%) had a normal treadmill exercise stress test. These data indicate that complete myocardial revascularization can be effectively accomplished by this aggressive surgical approach in patients with severe coronary artery disease with low mortality and morbidity; high patency rates of conduits and anastomoses can be achieved with excellent early clinical results on follow-up.

(Am J Cardiol 1990;66:651–659)

Today's cardiovascular surgeons are frequently challenged by patients with severe, diffusely diseased coronary arteries. In the Coronary Artery Surgery Study, approximately 5% of patients were said to have no graftable arteries.[1] Complete myocardial revascularization of such patients would require an aggressive, time-consuming surgical approach, which includes long coronary arteriotomy, coronary endarterectomy and reconstruction, and multiple bypass grafting. Modern myocardial protection using standard blood cardioplegia and/or enriched blood cardioplegia enables surgeons the time to perform this extensive operation. Thus, this study evaluates the efficacy and safety of such a surgical approach and analyzes early postoperative results by symptomatology, treadmill testing, angiography and other clinical parameters.

METHODS

Study population: AGE, SEX AND RISK FACTORS (TABLE I): Within a 2.5-year period (October 1985 and April 1988) 130 patients underwent long coronary arteriotomy, endarterectomy and reconstruction combined with multiple bypass grafting using a combination of saphenous vein and internal mammary artery conduits. Of these, 114 were men (88%) and 16 were women (12%) (mean age 64 years, range 35 to 84); 34 patients (26%) were >70 years old. With regard to risk factors, 24 patients (19%) had diabetes and 63 (49%) had history of ≥1 myocardial infarctions before surgery; 11 patients had history of acute myocardial infarction within 2 weeks before the surgical procedure. Twenty-five patients (20%) required either first or second repeat operations. Before surgery, the great majority of the patients had accelerating (unstable) angina or acute myocardial

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From the Northern California Heart and Lung Institute, Mt. Diablo Hospital Medical Center and the California Heart Medical Group, Concord, California. Manuscript received March 12, 1990; revised manuscript received May 10, 1990.

Address for reprints: Rolf G. Sommerhaug, MD, Northern California Heart and Lung Institute, 2540 East Street, Concord, California 94520-1960.

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TABLE I Clinical Characteristics

Total patients	130	
Men	114	(88%)
Women	16	(12%)
Age range (mean) (yrs)	35–84 (64)	
Elderly patients >70 years old	34	(26%)
Risk factors		
Diabetes mellitus	24	(19%)
Cigarette smoker	74	(57%)
Hypertension (systolic >150, diastolic >90)	73	(56%)
Family history of coronary disease	47	(36%)
Hyperlipidemia (cholesterol >200, triglycerides > 150)	38	(29%)
Previous myocardial infarction	63	(49%)
Acute myocardial infarction <2 weeks	11	(9%)
Prior coronary bypass surgery	25	(19%)
Medications		
Antianginal medication	126	(97%)
Calcium blockers	94	(72%)
Beta blockers	56	(43%)
Diuretics	36	(28%)
Nitrates	38	(29%)
Nitroglycerin	83	(64%)
None	4	(3%)
Electrocardiographic findings		
Old myocardial infarction	58	(45%)
ST changes	72	(55%)
Left bundle branch block	6	(5%)
Chest x-ray		
Normal	83	(64%)
Cardiomegaly mild to moderate	37	(28%)
Not available	10	(8%)

infarction; 93 patients (72%) were in the former category while 7 (5%) were in the latter.

Angina classification and exercise testing: Based on the Canadian Cardiovascular Society Angina classification,[2] 118 patients (91%) were in class III or IV, whereas only 12 were in class I or II. Thirty-seven patients (28%) had enlarged cardiac silhouette on chest x-ray (Table I). Sixty-two patients underwent preoperative treadmill stress testing: 57 (92%) had abnormal, 1 had equivocal and 2 had normal results, and 2 had ventricular arrhythmias. Of the 57 patients with abnormal stress tests, 3 developed hypotension during the test. One hundred and twenty-six patients (97%) were taking antianginal medication and/or diuretics preoperatively. Only 4 patients (3%) were not taking cardiac medications.

Hemodynamic and angiographic data (Table II): Coronary angiography revealed severe diffuse disease in most patients, with multiple hemodynamically significant lesions in both primary and secondary vessels. In contrast to simple 3-vessel coronary artery disease and 3-vessel bypass, these patients required 4 to 5 coronary anastomoses to each primary system of vessels to accomplish adequate revascularization. In addition, many of these patients had viable myocardium and total atherosclerotic occlusion of the entire length of the primary vessel without angiographically visible secondary branches. One hundred and eighteen (91%) had diffuse involvement of 3 arteries and 41 patients (32%) had >50% left main coronary artery disease. The mean Friesinger angiographic score[3] was 12; 108 patients (83%) had an angiographic score of ≥10.

TABLE II Angiographic and Hemodynamic Data

Number of diseased arteries coronary arteries narrowed in diameter >50%		
I	3	(2%)
II	9	(7%)
III	118	(91%)
Left main disease >50% diameter narrowing	41	(32%)
Angiographic score based on Friesinger's criteria	(108)	(83%)
10	11	(10%)
11	27	(25%)
12	49	(45%)
13	20	(19%)
14	1	(0.1%)
Pulmonary artery wedge pressure >15mm Hg (74)	41	(57%)
Ejection fraction (120)		(92%)
<0.50 and >0.41	21	(18%)
<0.40 and >0.20	18	(15%)
<0.20	2	(2%)
Cardiac index <2.0 liters/min/m^2 (59)	6	(5%)

Left ventricular end-diastolic pressure or pulmonary capillary wedge pressure was obtained in 74 patients and was elevated (>15 mm Hg) in 41 (55%). Cardiac index was available in 59 patients, and was <2 liters/min/m^2 in 6 patients (10%). Planographic ejection fraction was available in 120 patients; in 41 patients the ejection fraction was <50%. Eighteen of the 41 patients had an ejection fraction ≤40%, and 2 had an ejection fraction <20%.

Surgical procedure: Under general anesthesia and careful hemodynamic and electrocardiographic monitoring, a median sternotomy was performed and the right atrium and ascending aorta were cannulated. With the patient on cardiopulmonary bypass, myocardial protection was accomplished using blood cardioplegia core cooling and topical cold saline solution maintaining myocardial temperature at 15°C.[4,5] Enriched blood cardioplegia was used in patients with poor left ventricles and in those with acute infarction.

Long coronary arteriotomy (5 to 12 cm), endarterectomy and reconstruction were performed in 152 coronary systems. Multiple branch procedures in a coronary artery was only counted as single system endarterectomy. Endarterectomy and reconstruction of the left anterior descending (LAD) system (LAD proper, diagonal and septal branches) were performed in 121 patients; of the circumflex system (circumflex proper and obtuse marginal branches) in 13 patients; and of the right coronary system (the right main coronary artery and branches beyond the crux) in 18 patients. Single system endarterectomy and reconstruction were performed in 109 patients, double in 20 and triple in 1. In addition to coronary endarterectomy and reconstruction, multiple bypass grafting was performed with a mean graft rate of 9 (range 2 to 18). A combination of saphenous veins and internal mammary arteries were used as conduits.

Our method of endarterectomy is the exact dissection and removal of the atherosclerotic plaque extending from the primary coronary vessel into the secondary branches feeding the myocardium. These plugs commonly extend only 1 to 2 cm and are easily removed once the plane is developed. The emphasis is on dissection rather than forceful extraction using a modification

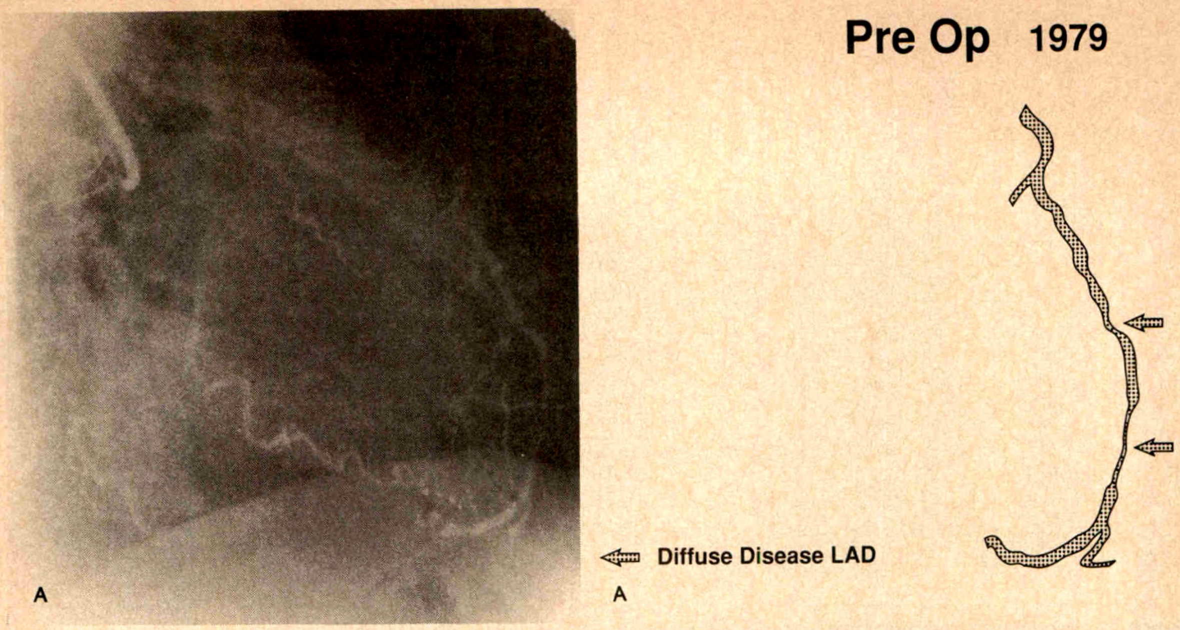


FIGURE 1A. Coronary angiogram *(left)* and schematic drawing *(right)* illustrating diffuse disease in distal half of left anterior descending (LAD) artery before first bypass operation in 1979.

of Dr. Noel Mills' instruments. The wide open mouth of secondary branches completes the endarterectomy phase. Reconstruction of the coronary artery consists of lengthwise closure of the arteriotomy with a venous graft. The graft is commonly tapered lengthwise to minimize the ectasia effect. To decrease thrombogenicity and potential early graft failure, direct bypass to the mouth of secondary branches within the endarterectomy bed using sequential graft technique rather than long venous anastomosis is a recent technical modification. When the endarterectomy only involves the proximal half of the coronary artery, the artery was bypassed distally beyond termination of the plaque to prevent dissection of the intimal flap. The aortic cross clamp time ranged from 58 to 304 minutes (mean 173). The cardiopulmonary bypass time ranged from 95 to 366 minutes (mean 242).

Follow-up clinical parameters: Operative mortality and morbidity were carefully examined in this series of patients. Perioperative myocardial infarction was determined by electrocardiographic appearance of new Q waves or loss of anterior R waves in combination with elevated creatine kinase-MB enzymes. In addition, the postoperative use of pharmacologic (that is, inotropic agents) and mechanical (that is, intraaortic balloon counterpulsation) support was also reviewed. Clinical

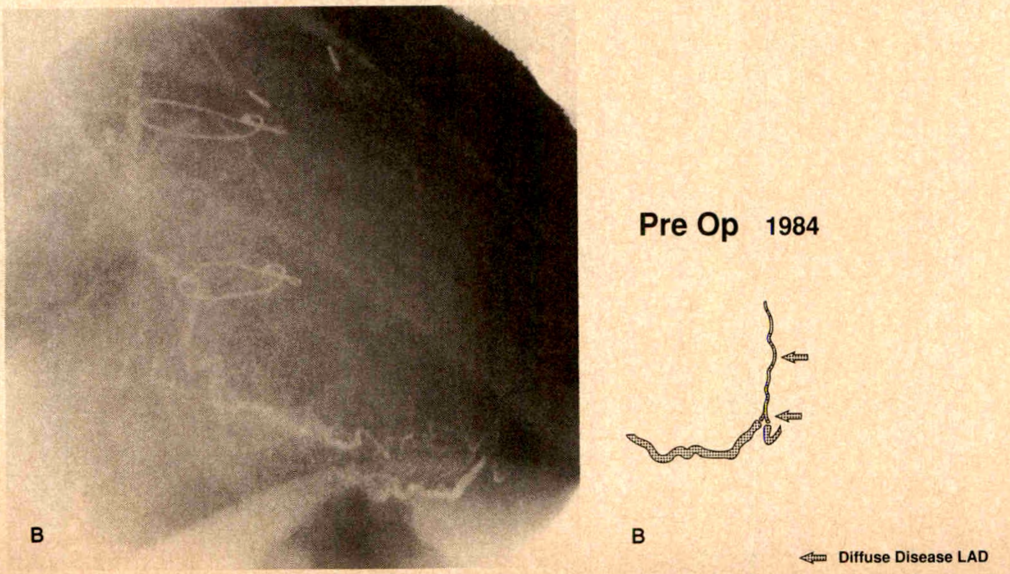


FIGURE 1B. Coronary angiogram *(left)* and schematic drawing *(right)* showing progression of diffuse disease in distal half of left anterior descending (LAD) before second bypass operation in 1984.

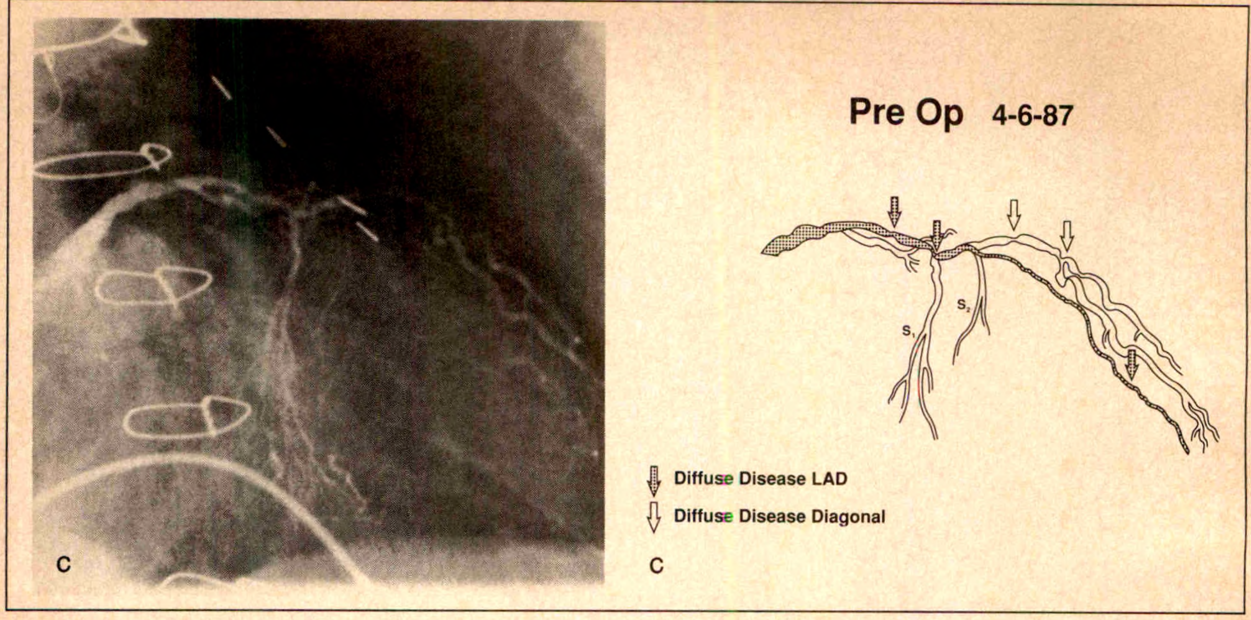


FIGURE 1C. Preoperative coronary angiogram *(left)* and schematic drawing *(right)* depicting a threadlike remnant of the proximal left anterior descending (LAD) distal to the second septal perforator.

follow-up, including short- and long-term mortality, morbidity, exercise treadmill testing and angiography, was assessed. Furthermore, we compared our surgical results based on previous identified risk factors according to the methods of Brenowitz et al[6] (age >70 years, repeat operations, insulin-dependent diabetes, female gender, and severe left ventricular dysfunction—that is, ejection fraction 0.10 to 0.35).

RESULTS

Case illustration (Figure 1): This series included several patients who required repeat operation because of early graft failure after ≥1 prior bypass operation. Figure 1 is a representative case of a 74-year-old man with class IV angina.

Operative mortality and morbidity (Table III): There were 3 surgical deaths (2.3%) among the 130 patients.

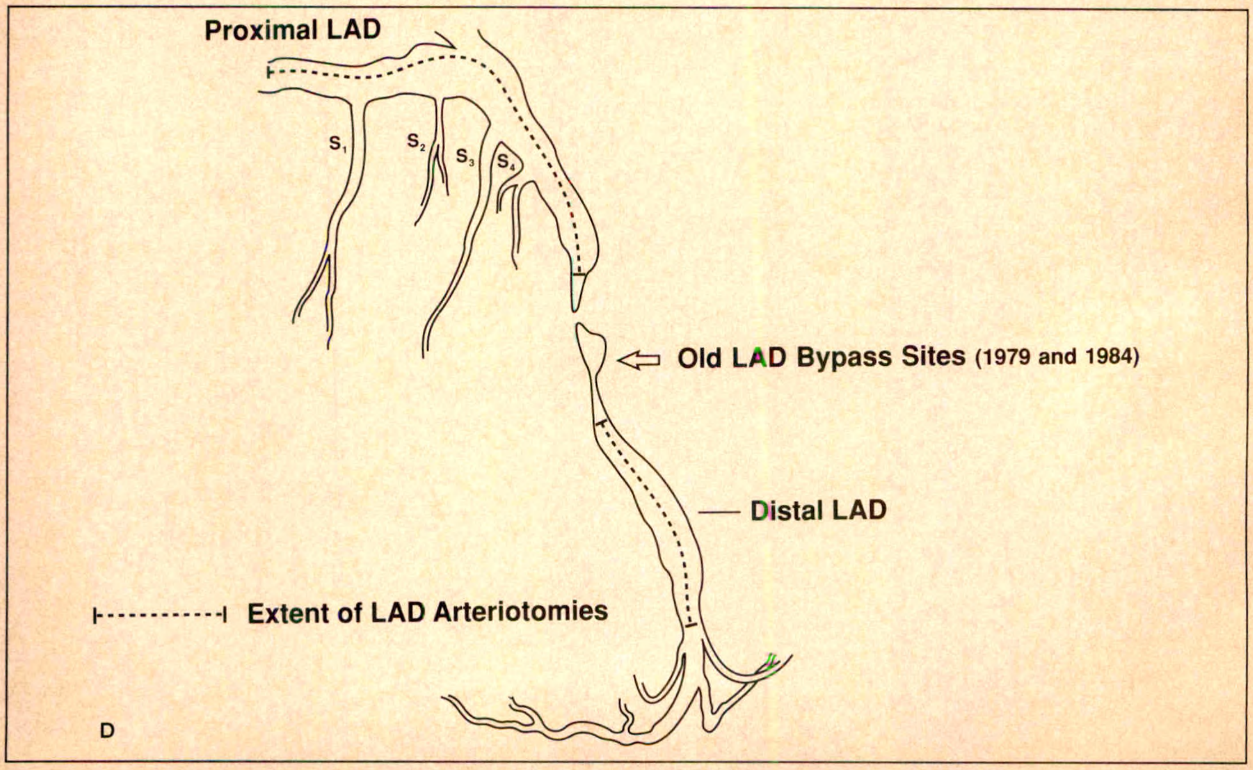
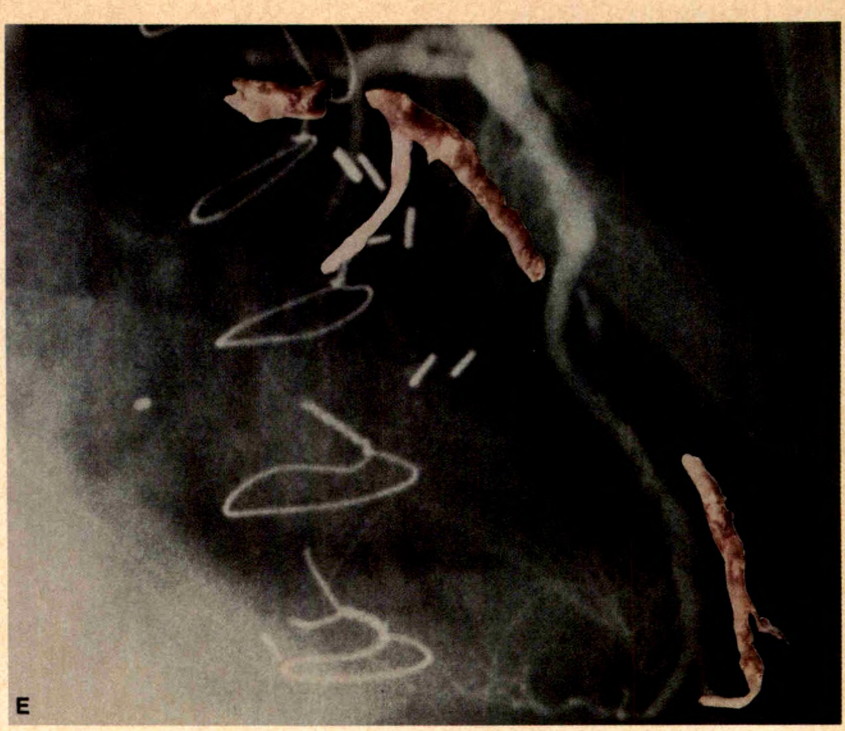

Proximal LAD
S1
S2
S3
S4
Old LAD Bypass Sites (1979 and 1984)
Distal LAD
Extent of LAD Arteriotomies
D

FIGURE 1D. Schematic drawing showing length and extent of proximal and distal left anterior descending (LAD) arteriotomies *(dashed line)*.

FIGURE 1E. Photograph of the endarterectomy specimen from proximal and distal left anterior descending (LAD) artery superimposed on the postoperative coronary angiogram shown in Figure 1F.



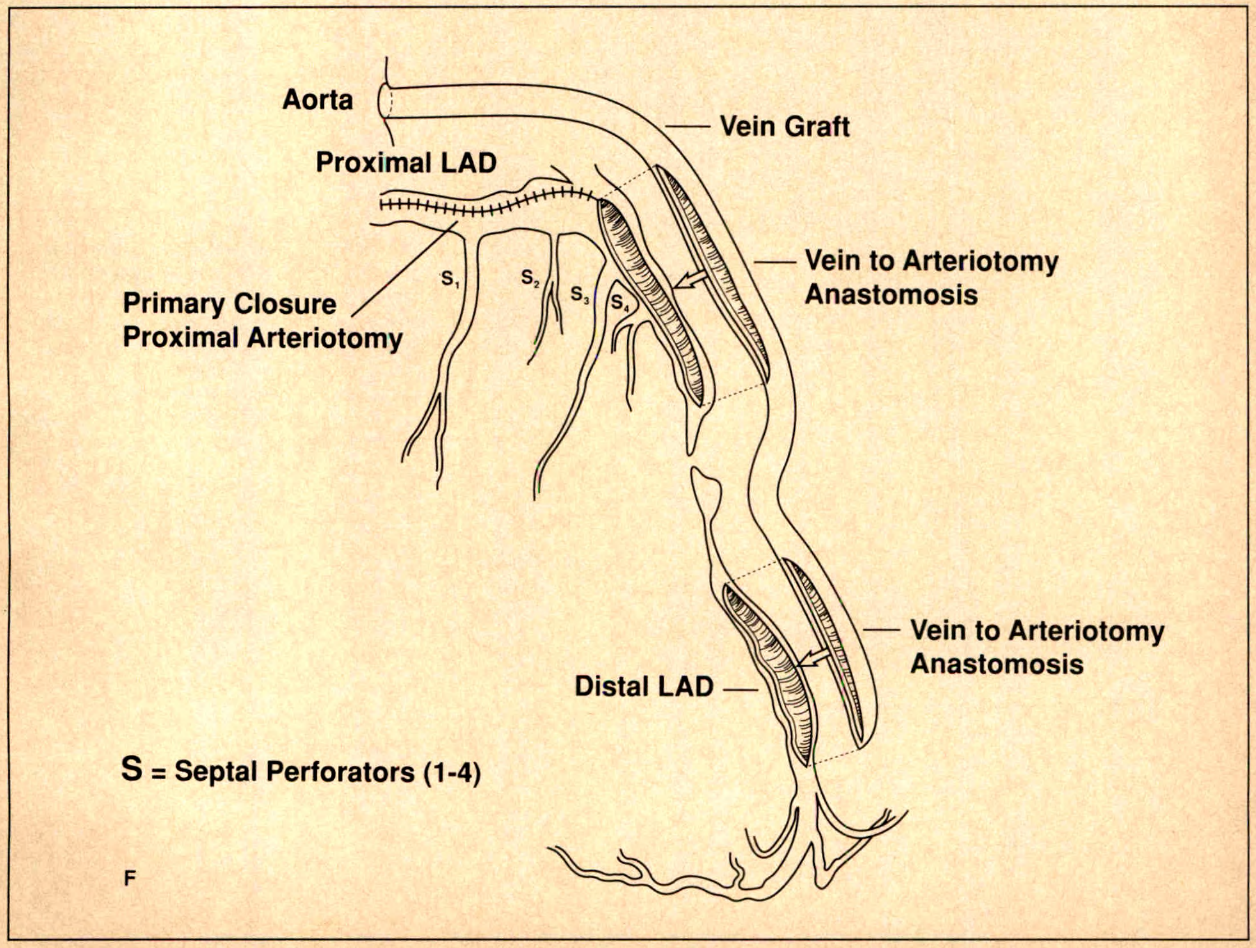

Aorta
Vein Graft
Proximal LAD
Vein to Arteriotomy Anastomosis
Primary Closure Proximal Arteriotomy
S_1
S_2
S_3
S_4
Vein to Arteriotomy Anastomosis
Distal LAD
S = Septal Perforators (1-4)
F

FIGURE 1F. Schematic drawing showing saphenous vein reconstruction of left anterior descending (LAD) artery after completion of proximal and distal endarterectomy.

Two of the deaths were from cerebral vascular accidents, probably as a result of cerebral anoxia or embolization, and the third patient died from myocardial failure. Two other patients had perioperative myocardial infarction (1.5%) demonstrated by electrocardiographic changes and cardiac enzyme elevation.

Based on identified risk factors in accordance to Brenowitz et al,[6] 30-day mortality in our study was 0% in patients with none of these risk factors, 3.4% with 1, and 5.5% with ≥2 risk factors (Table III). Other complications include 2 patients with minor cerebral vascular accidents who recovered without residual neurologic deficit, and 2 with sternal dehiscence that required rewiring of their sternum. In addition, the following minor complications were observed: 3 returned to the operating room for control of bleeding, 5 developed pleuropericarditis and all but 1 necessitated treatment with steroids, 2 had transient brachial plexus injury and recovered, and 9 had minor infections of the venous donor site in the leg and were treated with antibiotics.

Postoperative pharmacologic and mechanical support: Seventeen patients (13%) were treated postoperatively with dopamine for <12 hours, and 13 (10%) were given dopamine for 12 to 24 hours. Three patients required dopamine for >24 hours in order to enhance cardiac output and improve renal perfusion. Only 3 patients were on intraaortic balloon support for 1 to 3 days postoperatively, and only 3 patients required longer respiratory support for >48 hours.

Clinical follow-up: As of December 1988, 126 of the 127 patients discharged from the hospital were available for clinical follow-up; only 1 patient was lost to follow-

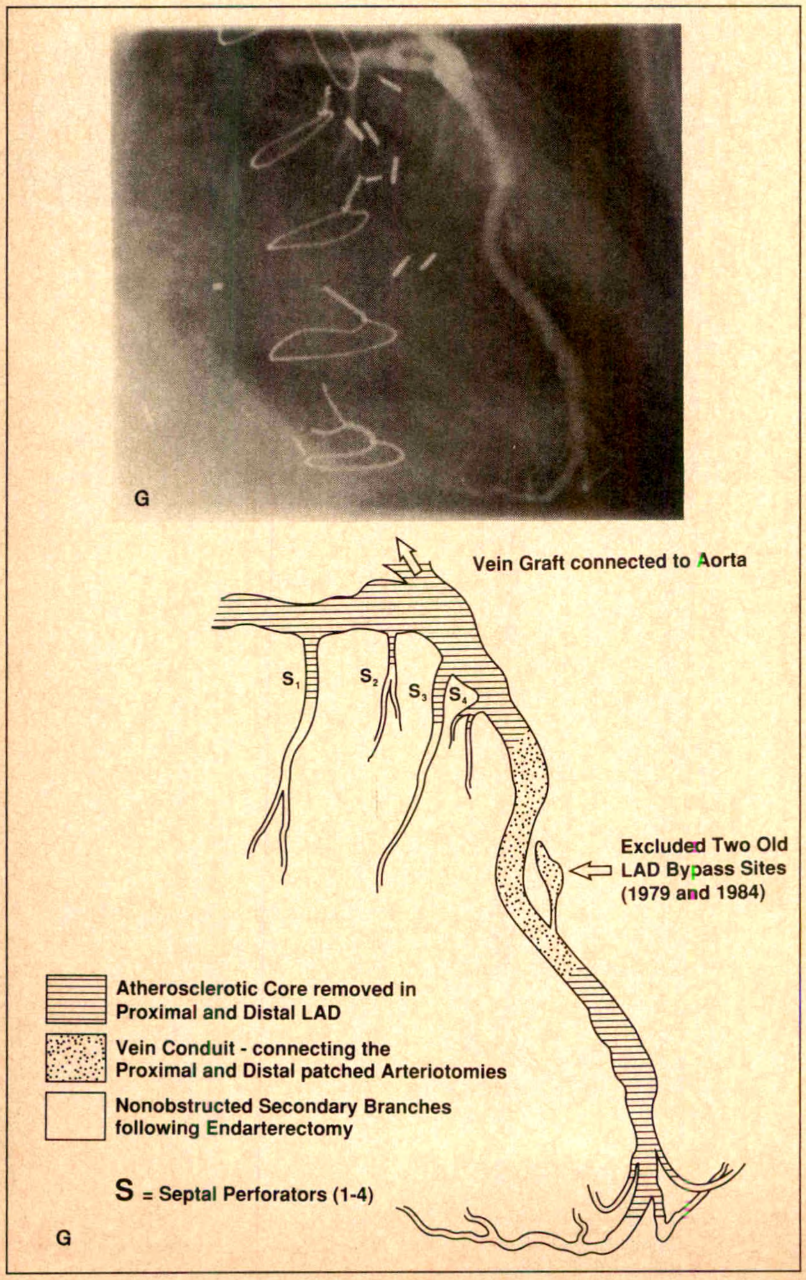

G
Vein Graft connected to Aorta
S1
S2
S3
S4
Excluded Two Old LAD Bypass Sites (1979 and 1984)
Atherosclerotic Core removed in Proximal and Distal LAD
Vein Conduit - connecting the Proximal and Distal patched Arteriotomies
Nonobstructed Secondary Branches following Endarterectomy
S = Septal Perforators (1-4)
G

FIGURE 1G. Postoperative coronary angiogram (4/20/87) *(top)* and schematic drawing *(bottom)*. The coronary atherosclerotic core was removed from the proximal and distal left anterior descending (LAD) artery, and a vein graft was connected to the proximal and distal patched arteriotomies. The left anterior descending coronary artery has now been reconstructed.

TABLE III Thirty-Day Mortality—121 Patients—Left Coronary Endarterectomy

No. of Risk Factors	30-Day Mortality	p Value
0	0/45 (0%)	NS
1	2/58 (3.4%)	NS
>2	1/18 (5.5%)	NS
Total	3/121 (2.5%)	

NS = not significant.

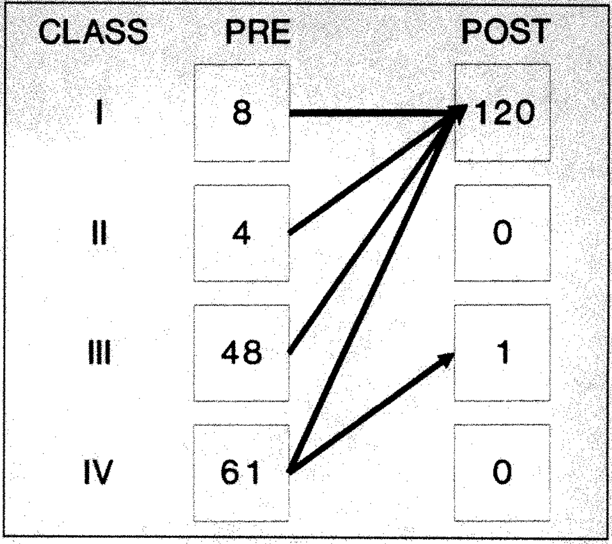


FIGURE 2. Pre- and postoperative angina classification in this study group according to the Canadian Cardiovascular Society Criteria.

up. This represented a clinical follow-up of 2,525 patient months. The mean follow-up was 20 months. Five patients died after hospital discharge between 4 and 30 months. Only 1 of these patients, who had a history of ventricular arrhythmias and was taking flecanide, died from probable cardiac arrest. The remaining causes of deaths were noncardiac-related, which included cerebral vascular accident, peritonitis from a perforated colon, metastatic carcinoma to the brain (melanoma) and carcinoma of the colon. Of the 126 patients discharged, 121 were alive for a survival rate of 96%. Of these 121 patients, 120 (99%) were in angina class I by the Canadian Cardiovascular Society Classification, and the remaining 1 (0.8%) was in angina class III (Figure 2).

Early angiographic follow-up (Figure 3): Twenty-four postoperative patients were studied angiographically within 20 days after surgery. These patients were selected at random and underwent study after signing a written consent. Nine of these patients (37%) were undergoing first or second repeat operations. Of 206 coronary anastomoses studied, 202 were patent for a patency rate of 98%; these anastomoses were from a total of 69 conduits of which 68 were patent for a patency rate of 98%. Thirty-two of 33 conduits to endarterectomized and reconstructed vessels were patent for patency rate of 97%.

Seventeen of the 24 patients underwent preoperative and postoperative ventriculography for analytic comparison. The global ejection fraction at rest was calculated by the planographic method in the right anterior oblique position. When allowing for 5% technical variance, 8 had improvement by an average of 13%, 8 had no change and 1 was worse. In the latter case, a perioperative apical infarction occurred probably as a result of an embolus from an old left anterior descending graft; all recently placed grafts and anastomosis were patent in this patient who was completely asymptomatic 14 months after surgery.

Late angiographic follow-up: Three postoperative patients underwent late repeat studies up to 36 months because of symptoms suggesting angina. The first patient's endarterectomy site was patent and all 10 anastomoses and grafts were also patent. The second patient had patency in 8 of 9 anastomoses; the only exception was an occlusion of the graft to the proximal left anterior descending endarterectomy site. The third had patency in all 7 anastomoses and grafts. He developed a discreet 60% obstruction in the endarterectomized distal right coronary artery in which balloon angioplasty was performed. Thus, in the 3 patients who developed symptoms, 25 of 26 grafts and anastomoses were patent; only 1 graft closed.

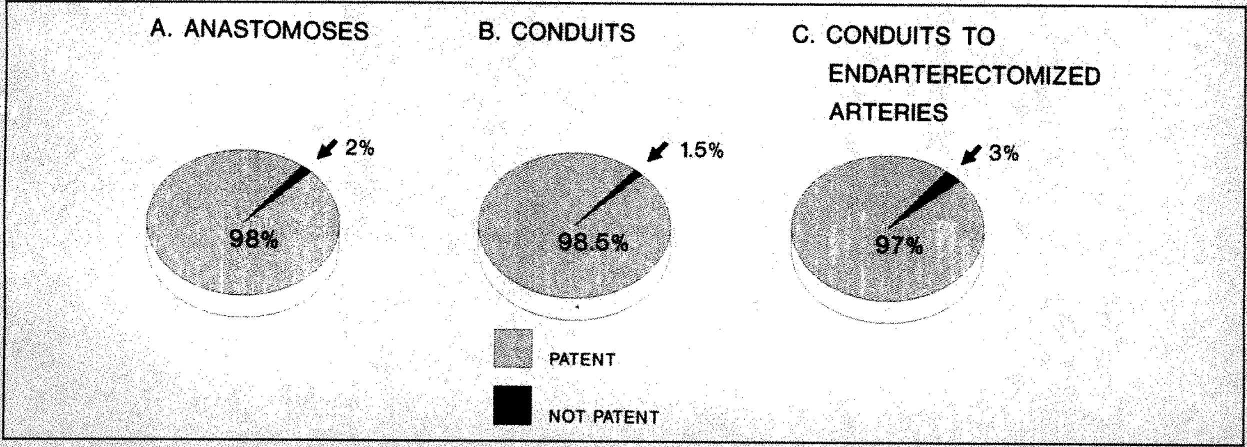


FIGURE 3. Patency rate for coronary anastomoses, conduits (veins or internal mammary arteries), and conduits to endarterectomized coronary arteries in patients electively studied after surgery.

Follow-up exercise treadmill testing (Figure 4): Seventy-one patients underwent postoperative treadmill stress tests with or without thallium scintigraphy; 63 (89%) were normal and 8 (11%) were abnormal (>1 mm ST-segment changes and/or abnormal thallium scintigraphy). In the 8 patients who had abnormal exercise test results, 4 were asymptomatic with less positive ST-segment changes from their preoperative exercise tests, 1 had improved thallium scintigraphy and 1 had ST changes despite graft patency. Two patients had no preoperative tests to compare.

In a subset of 29 patients in whom exercise testing was compared both before surgery and after coronary endarterectomy, reconstruction and bypass grafting, results of tests in 23 patients (79%) had converted from abnormal (>1 mm ST-segment depression) to normal, and another 6 (21%) had improvement (that is, less ST-segment depression) on repeat testing. Thus, all 29 patients were asymptomatic and had improved or normal studies on repeat exercise testing.

DISCUSSION

This study demonstrates that multiple bypass grafting and adjunct coronary endarterectomy and reconstruction can yield excellent clinical results and can be performed with low perioperative myocardial infarction (1.5%) and mortality rates (2.3%). These complication rates for coronary endarterectomy and reconstruction and multiple bypass grafting are comparable to the mortality and morbidity rates for conventional elective bypass grafting without coronary endarterectomy.[7] Furthermore, these low complication rates were achieved in patients with severe diffuse coronary artery disease and compromised left ventricular function. Moreover, approximately 50% of surgical candidates had sustained a prior myocardial infarction and about 20% were undergoing repeat operations.

The value of adjunct coronary endarterectomy and reconstruction is perhaps best exemplified by many patients in our series who had early graft failures after previous bypass operations (Figure 1). In this decade, with the exception of one recent small series[8] of 37 patients (average 3.2 bypass grafts) that reported a 2.7% perioperative infarction rate and 2.7% mortality rates, perioperative infarction rate in larger series of patients undergoing endarterectomy and bypass grafting varied between 4.9 and 16% and mortality rates from 2.3 to 15%.[9–14] The improved statistics in our series are possibly attributed to improved surgical technique and better myocardial protection. Blood cardioplegia affords excellent protection when administered carefully and with attention to detail.[4,5] Blood cardioplegia can be fortified with substrate if depletion of myocardial energy reserve is suspected. Furthermore, coronary endarterectomy and reconstruction were generally done last, again to optimize myocardial protection by infusing the blood cardioplegia solution through the aortic arch and grafts as they are anastomosed.

The importance of complete revascularization of the ischemic myocardium in patients with coronary artery disease is emphasized in this study. It is well known that good clinical outcome, freedom from repeat operation, and survival are adversely affected by incomplete revascularization.[15–19] In 1 report, which followed 500 surgical patients for 10 to 12 years, the presence of disease in ungrafted arteries was the most significant predictor of late cardiac events, including cardiac related deaths, recurrence of angina, myocardial infarction and repeat surgery.[15] In contrast to other investigations,[9–12] 80% of coronary endarterectomy and reconstruction were performed in the left anterior descending artery and its branches. Excluding left main disease, proximal left anterior descending occlusions (proximal to septal perforators) have the highest risk for sudden death, and frequently can leave surviving patients functionally incapacitated. Because residual lesions in the left anterior descending coronary artery after surgery is the most important predictor of late cardiac death,[16] revasculariza-

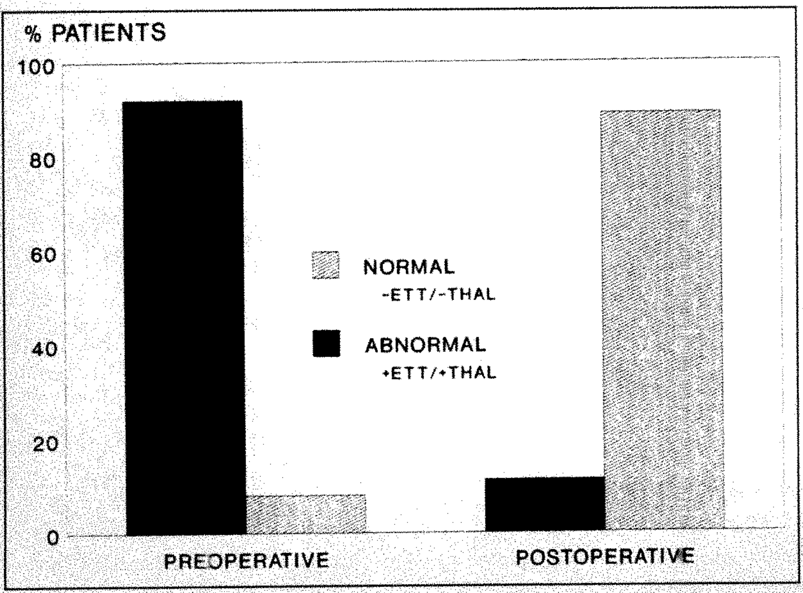


FIGURE 4. Pre- and postoperative exercise treadmill test (ETT) and/or thallium scintigraphy (THAL) results of patients from this study population.

tion of the entire myocardium served by major obstructive coronary arteries, and in particular the left anterior descending artery, is the fundamental goal of coronary bypass surgery.

In a recent article by Brenowitz et al,[6] it was demonstrated that patients with ≥ 2 risk factors had a significantly higher mortality (22.9%) when left coronary endarterectomy was performed. However, we found no significant increase in 30-day mortality in our patients when comparing 0, 1 and ≥ 2 risk factors. Since endarterectomy and reconstruction predisposes the artery to increased thrombogenic and embolic risk, particularly before the neointima is formed, modification of our technique of closure of the endarterectomy site, which excluded most of the raw surface area, has helped us eliminate these potential problems. Furthermore, distal grafting improves patency by preventing dissection of the intimal flap. Indeed, the early patency rate for coronary anastomoses (98%), conduits (99%) and conduits to endarterectomized and reconstructed arteries (97%) compares very favorably with early patency rates of 83%[20] to 89%[6] in other reports.

Perhaps the major limitation of this study is the lack of more long-term postoperative angiographic studies. We are currently making efforts to restudy as many patients as we can, but it has been difficult primarily because of economic factors, and because nearly all (99%) patients were asymptomatic in angina class I by the Canadian Cardiovascular Society classification. However, in the 3 patients who developed symptoms suggestive of angina and were subsequently studied angiographically up to 36 months, 25 of 26 grafts and anastomoses were patent and only 1 graft closed.

Among those postoperative patients who underwent exercise testing, 89% had a normal exercise test result. This was comparable with our previous reported result (95%) after multiple coronary grafting for diffuse disease.[19] A recent study reported 87% postoperative patients were angina free at 1 year with a yearly decrease of 6%; at 48 months, 67% were angina free.[6] Other investigators had reported late occurrences of angina at 9.1% per patient year, with 47% of patients free of angina at 6 years.[12] However, another series revealed that 50% of patients were angina free at 5 years.[10] With regard to left ventricular function in this series, 94% of patients had improved or unchanged ejection fractions at rest. Again this was comparable to other published series (73 to 77%).[13,14,21] Segmental wall motion analysis with respect to endarterectomy site is currently being investigated.

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Long-Term Results of Successful and Failed Angioplasty for Chronic Total Coronary Arterial Occlusion

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The results over a mean period of 2 years of successful percutaneous transluminal coronary angioplasty (PTCA) in 100 consecutive patients with chronic total coronary occlusion were compared with those in 100 consecutive patients whose PTCA was unsuccessful. The groups were comparable in terms of gender, age and arteries attempted. A control angiography in the group with successful PTCA was performed in 62 patients and showed a restenosis in 28 (45%). Repeat PTCA was performed in 21 versus 1 patient with failed PTCA ($p < 0.0001$). At follow-up, in the group with successful PTCA, there were 57 symptom-free patients versus 26 patients in the group with failed PTCA ($p < 0.0001$). Coronary artery bypass surgery was performed in 7 versus 37 patients ($p < 0.0001$), and there were 5 versus 3 deaths (difference not significant), respectively. In the group with successful PTCA, 27 of 82 patients (33%) had positive stress test results, compared with 49 of 85 patients (58%) in the group with unsuccessful PTCA ($p < 0.001$). The double product (beats/min × mm Hg/100) in patients with successful PTCA improved from 247 ± 57 before PTCA to 277 ± 61 ($p < 0.001$) at follow-up, whereas it did not significantly change in patients with failed PTCA. The work load (W) in patients with successful PTCA improved from 95 ± 34 before PTCA to 124 ± 40 at follow-up ($p < 0.001$). In patients with failed PTCA, work load improved less significantly, from 98 ± 37 before PTCA to 108 ± 34 at follow-up ($p < 0.05$). Thus, up to a mean of 2 years, patients with successful coronary angioplasty of chronic total coronary occlusion appeared to fare better than those whose angioplasty was unsuccessful.

(Am J Cardiol 1990;66:660–662)

Despite a moderate success rate, recanalization of chronic total coronary occlusion by percutaneous transluminal coronary angioplasty (PTCA) has become an accepted procedure in selected patients with a viable pertinent myocardial area.[1–4] A whole armamentarium of new devices are being developed, from laser to different vascular drills. However, only limited data are available to document a long-term benefit from the recanalization of chronic coronary occlusion. This study compares functional results in patients with successful PTCA of chronic total occlusion with those of patients with a failed attempt.

METHODS

Patients: The study population was composed of consecutive patients undergoing PTCA for recanalization of a chronic total coronary occlusion at our institution (Table I). Patients with successful PTCA were compared with patients with a failed attempt. Enrollment stopped in each group at 100 patients. Mean time of the occlusion was 3 ± 5 months in the group with successful PTCA and 5 ± 9 months in the group with failed PTCA (difference not significant [NS]). These figures are based on 59 patients in the first and 61 patients in the second group for whom the time of occlusion could be determined with sufficient reliability. Erect bicycle stress tests or supine bicycle radionuclide stress tests were performed before and after PTCA and at follow-up, as previously described.[5]

Percutaneous transluminal coronary angioplasty: Typical indications for PTCA were angina or positive results on stress testing, or both, with a suitable coronary anatomy for recanalization.[6] Chronic total coronary occlusion was defined as interruption of the angiographic vessel continuity without anterograde flow (Thrombolysis in Myocardial Infarction Trial grade 0). Successful recanalization was defined as an angiographic stenosis of <50% (estimated diameter reduction) after PTCA. Multivessel PTCA was defined as angioplasty of ≥2 vessels, with presence of a total occlusion in ≥1 of the vessels involved. Primary success per patient was considered to be present if all of the following criteria were met: (1) angiographic improvement (residual stenosis <50%) of all lesions or at least the total chronic occlusion, (2) absence of cardiac complication including myocardial infarction by electrocardiographic (Q wave) or enzymatic evidence (creatine kinase value >3 times normal) and need for emergency bypass surgery, and (3) improvement in angina symptom class of ≥1 by the Canadian Cardiovascular Society or in stress test performance, or both.

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All patients received aspirin before PTCA. Most patients were given intracoronary nifedipine or nitrates, or both, immediately before and 100 mg/day of aspirin after angioplasty. Coronary angioplasty was performed using a steerable balloon catheter according to the modified technique for total occlusion.[6] In 47 patients, the occluded vessel was not the only vessel attempted. In patients with total occlusion who underwent successful PTCA, 23 had 1 and 1 had 2 additional vessels attempted, with success in ≥1 additional vessel in 20 patients. In patients with failure regarding the total occlusion, 17 had 1 and 6 had 2 additional vessels attempted, with success in ≥1 additional vessel in 17 patients. Restenosis was defined as a luminal diameter narrowing of ≥50% at the site of successful PTCA on a control angiogram.

Follow-up: All patients underwent follow-up examination. The follow-up period was 24 ± 14 months (range 6 to 54) and 21 ± 13 months (range 1 to 41) in patients with successful and unsuccessful PTCA, respectively. A follow-up stress test was done in 82 and 85 patients in the 2 groups, respectively. For the patients who underwent bypass surgery, the stress test result before operation was analyzed. For all other patients, the latest available stress test result, even if they underwent repeat PTCA, was analyzed. A follow-up angiography was performed in 62 of 100 patients with successful angioplasty at 14 ± 7 months (range 6 to 26) after the last PTCA.

TABLE I Patient Characteristics

	Success (n = 100)	Failure (n = 100)
Men	93	88
Age (yrs)	55 ± 11	55 ± 12
range	45–71	37–79
PTCA		
1 artery	68	78
>1 artery	24	23
Duration of occlusion (mo)	3 ± 5 (n = 59)	5 ± 9 (n = 61)
Arteries		
LAD	54	44
Right	25	38
LC	21	18

No significant differences for the 2 groups.
LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; PTCA = percutaneous transluminal coronary angioplasty.

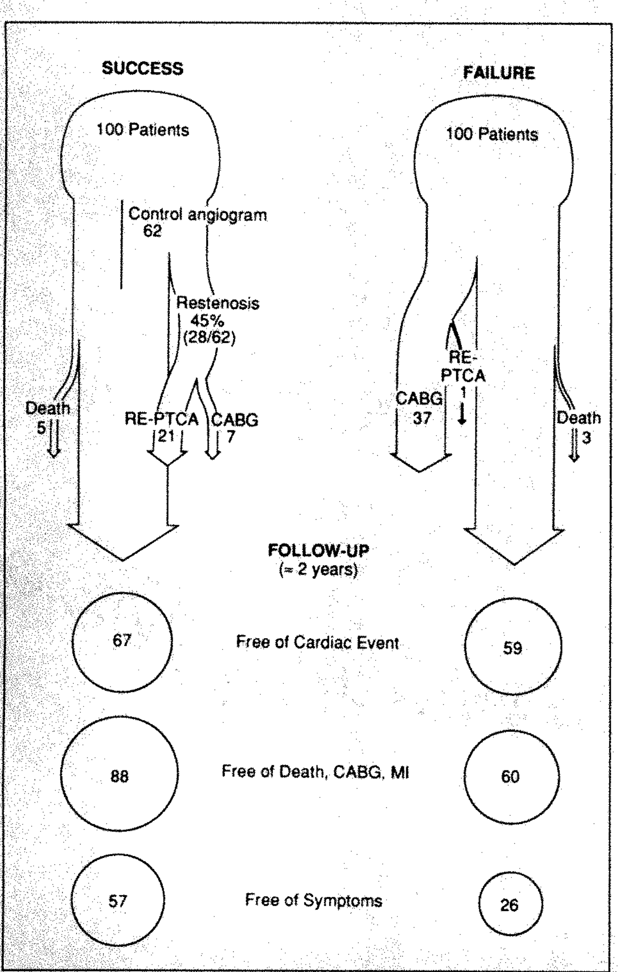

FIGURE 1. Outcome after successful and failed percutaneous transluminal coronary angioplasty (PTCA) for chronic total occlusion. CABG = coronary artery bypass grafting; MI = myocardial infarction; RE-PTCA = repeat or new percutaneous transluminal coronary angioplasty.

Statistics: Statistical analyses were performed using Student's *t* test for comparison of group means, and chi-square test for comparison of discrete variables. Values are mean ± standard deviation.

RESULTS

Cardiac events: Figure 1 shows the follow-up data of the groups. A control angiogram in 62 patients in the group with successful PTCA showed a restenosis in 28 patients (45%). There were 21 additional PTCAs in this group compared with 1 in the group with unsuccessful PTCA (p <0.0001); 7 versus 37 patients had elective bypass surgery (p <0.0001), and there were 5 versus 3 deaths (NS), respectively.

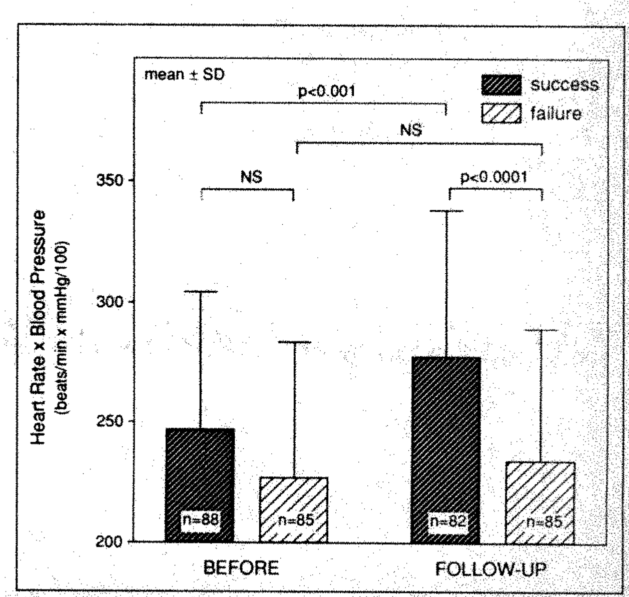

FIGURE 2. Double product (heart rate × blood pressure in beats/min × mm Hg/100) during stress testing in patients before successful versus failed percutaneous transluminal coronary angioplasty of chronic total occlusion and at follow-up. NS = not significant; SD = standard deviation.

Angina status: At follow-up in the group with successful PTCA, there were 57 angina-free patients compared with 26 patients in the group with failed PTCA ($p < 0.0001$); 12 versus 16 patients were in Canadian Cardiovascular Society class I (NS), 19 versus 36 in class II ($p = 0.007$), 5 versus 13 in class III ($p = 0.05$) and 7 versus 9 in class IV (NS), respectively.

Stress test: In the group with successful PTCA, there were 27 patients (33%) with a positive stress test result, compared with 49 patients (58%) in the group with failed PTCA ($p < 0.001$). The double product (beats/min × mm Hg/100) in patients with successful PTCA improved from 247 ± 57 before PTCA to 277 ± 61 at follow-up ($p < 0.001$), whereas it did not improve significantly in patients with failed PTCA (227 ± 56 before PTCA and 234 ± 55 at follow-up) (Figure 2). The work load in patients with successful PTCA improved from 95 ± 34 W before PTCA to 124 ± 40 W at follow-up ($p < 0.001$). In patients with failed PTCA, it also improved, although less significantly, from 98 ± 37 W before PTCA to 108 ± 34 W at follow-up ($p < 0.05$) (Figure 3).

DISCUSSION

There are several limitations to this study that are important to consider in order to put the results in context. This was not a randomized trial of angioplasty or no angioplasty in patients with chronic total coronary occlusion. Thus, there is no meaningful null hypothesis, and patients who had a successful angioplasty may indeed represent a lower risk patient group with an excellent functional and long-term outcome even if angioplasty had not been performed. Nevertheless, the groups appear well matched (Table I).

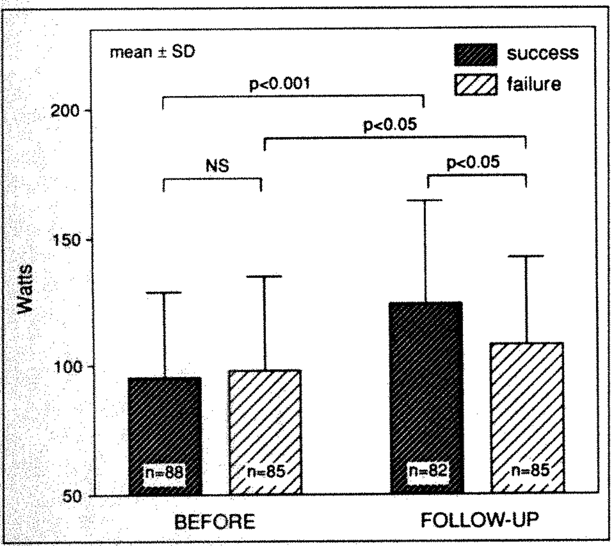

FIGURE 3. Work load (Watts) during stress testing in patients before successful versus failed percutaneous transluminal coronary angioplasty of chronic total occlusion and at follow-up. Abbreviations as in Figure 2.

There was clear-cut functional improvement in patients with successful PTCA for chronic total occlusion not only in angina class, but also in the results of the stress test. The incidence of major cardiac events was not significantly different in both groups. Bypass surgery was needed less frequently in the group with successful PTCA. However, they had a higher incidence of repeat PTCA. A patient with successful balloon recanalization of a chronic total occlusion has almost a 60% chance of being symptom-free at 2 years, a 20% chance of requiring repeat PTCA, and only a 7% chance of undergoing bypass surgery; this is in contrast to a patient with unsuccessful PTCA with only a 26% chance of being symptom-free and a 37% chance of needing bypass surgery. Patients with failed PTCA not referred for surgery continued to receive medical treatment, explaining, in part, the 58% rate of patients with positive stress test results at follow-up.

Most patients had PTCA of chronic total occlusion in 1 vessel and the functional outcome could clearly be linked to the result of PTCA. Successful PTCA of an additional vessel was performed in 37 patients, and improvement in some of them may have been due to recanalization of this additional vessel. However, these patients were distributed almost equally among the 2 groups (20 in the group with successful and 17 in the group with failed recanalization). Thus, they can be expected to exert a similar favorable influence on the functional result in both groups.

The major problem after successful balloon recanalization of chronic total occlusion is restenosis.[7] In our study, the restenosis rate was 45% in the two-thirds of the patients with follow-up angiography. Whether new devices such as intracoronary stents or lasers will diminish the restenosis rate remains to be seen.

At a mean of 2 years, there appears to be a functional benefit for patients who undergo successful compared with unsuccessful coronary angioplasty of chronic total occlusion, justifying the indications in retrospect.

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Emergency Percutaneous Transluminal Coronary Angioplasty for Acute Myocardial Infarction in Patients 70 Years of Age and Older

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Direct percutaneous transluminal coronary angioplasty (PTCA) was performed as the primary means of establishing reperfusion during acute myocardial infarction in 105 elderly patients (mean age ± standard deviation 75 ± 4 years) at a mean of 5.5 ± 4.0 hours from symptom onset. Fifty-two patients (50%) had anterior infarctions, 70 (67%) had significant narrowing in >1 vessel, and 12 (11%) were in cardiogenic shock. Primary success was achieved in 91% of the infarct-related arteries. Four patients with failed PTCA underwent emergency bypass surgery; 10 had early symptomatic reocclusion of the dilated vessel. There was 1 death acutely in the catheterization laboratory. The overall in-hospital mortality was 18%. Three-vessel coronary artery disease and cardiogenic shock on presentation were the strongest predictors of in-hospital death. Global ejection fraction improved from 54 ± 13 to 61 ± 15% ($p < 0.001$). The 1- and 5-year survival rates, including in-hospital deaths, were 73 and 67%, respectively. It is concluded that direct PTCA is an effective means of salvaging ischemic myocardium during acute myocardial infarction in the elderly patient. It is associated with a high success rate and low complication rate. The short- and long-term survival in this high-risk group of patients are improved compared with survival rates in historical controls.

(Am J Cardiol 1990;66:663–667)

The elderly have long been established as a high-risk group during acute myocardial infarction (MI) with high morbidity and mortality.[1-4] Trials using thrombolytic therapy generally exclude this group of patients because of a significantly higher incidence of hemorrhagic complications.[5,6] Direct percutaneous transluminal coronary angioplasty (PTCA) without prior use of thrombolytic agents has been shown to be very effective in opening occluded vessels during acute MI. Furthermore, direct PTCA is not commonly associated with significant hemorrhagic complications while reduced in-hospital mortality and improved left ventricular function at discharge have been demonstrated.[7-9] This report details our cumulative experience with direct PTCA for acute MI in 105 consecutive patients aged ≥70 years.

METHODS

Patient population: From November 1980 to March 1989, all patients presenting with the clinical diagnosis of acute MI were taken to the cardiac catheterization laboratory for emergency coronary angiography and PTCA (n = 614). The diagnosis of acute MI was based on (1) chest pain consistent with ongoing myocardial ischemia persisting >30 minutes, (2) ≥1 mm ST-segment elevation in ≥2 contiguous leads on the admission electrocardiogram, and (3) symptom duration of ≤6 hours. Patients with a "stuttering infarctional syndrome" presenting >6 hours but ≤24 hours after pain onset with ongoing pain, ST-segment elevation and preservation of electrocardiographic R waves in the infarct region were included. All patients fulfilling these criteria underwent direct PTCA as the only means of acute reperfusion therapy. No thrombolytic agents were administered before the procedure. Patients presenting with systolic blood pressure <80 mm Hg, with clinical signs of systemic hypoperfusion unresponsive to volume expansion, were classified as having cardiogenic shock.

Percutaneous transluminal coronary angioplasty protocol: An emergency cardiac catheterization team was on call 24 hours/day with the ability to commence catheterization from 30 to 45 minutes of patient presentation. In the emergency room, all patients were given 10,000 units of heparin, 75 mg of lidocaine intravenously followed by a continuous infusion, and aspirin 325 mg orally. In the laboratory, unless contraindicated by bradyarrhythmias or hypotension, 5 mg of verapamil was given intravenously and 5 mg of isosorbide dinitrate

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TABLE I Technical Results of Direct Percutaneous Transluminal Coronary Angioplasty

Infarct-Related Artery*	No. of Arteries	Primary Success
Left anterior descending	54	
Totally occluded		26
Subtotally occluded		23
Both		49 (91%)
Left circumflex	11	
Totally occluded		7
Subtotally occluded		3
Both		10 (91%)
Right coronary artery	39	
Totally occluded		21
Subtotally occluded		15
Both		36 (92%)
All vessels		
Totally occluded		54 (90%)
Subtotally occluded		41 (93%)
Both		95 (91%)

* One subtotal left main occlusion successfully dilated. See text.

was given sublingually. After assessment of left ventricular function, a low molecular weight dextran infusion was begun at the discretion of the operator and an additional 5,000 to 10,000 units of heparin administered.

Vascular access was obtained through the femoral artery and left ventriculography was performed in a 30° right anterior oblique projection. Angiography of the noninfarct artery was performed first, followed by angiography of the infarct-related artery. PTCA was performed with an over-the-wire system. Successful PTCA was defined as dilation of the infarct vessel to ≤40% residual stenosis. After the acute procedure, heparin, lidocaine and nitrates were continued for ≥48 hours. Aspirin, dipyridamole and a calcium antagonist were begun immediately after the procedure and continued as discharge medications. Serial electrocardiograms, total creatine kinase and isoenzymes were obtained in all patients.

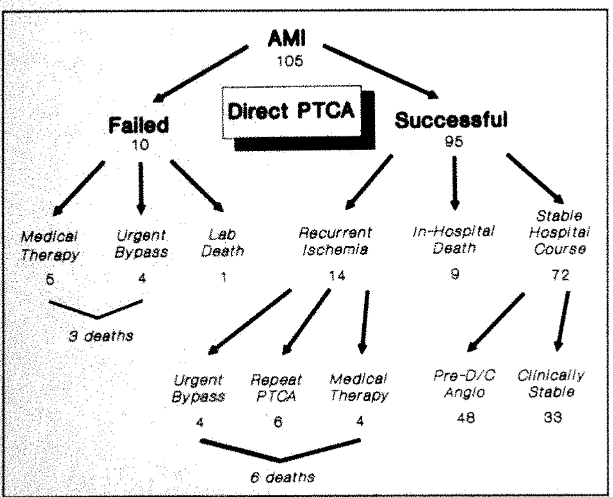

FIGURE 1. Flow diagram of the hospital course of patients treated with direct angioplasty. Pre-D/C Angio = predischarge angiogram; PTCA = percutaneous transluminal coronary angioplasty.

Follow-up: All patients with recurrent chest pain during the hospitalization were taken back to the catheterization laboratory for angiography. Angiography and ventriculography were performed in all consenting patients who survived to hospital discharge. Paired ventriculograms were available in 51 patients. A modified Dodge area-length method was used to calculate end-diastolic and end-systolic volumes. Computation of the ejection fractions was performed by a technician blinded to the clinical circumstances of the procedure. Follow-up information available through November 1, 1989, was obtained by questionnaire, telephone interview or office visit.

Statistics: The numerical results are expressed as mean values ± standard deviation. Statistical analysis from group means and mean differences were performed by 2-tailed Student's *t* test. Stepwise logistic regression was used to evaluate the relation of selected clinical variables to in-hospital mortality. Survival data are reported using the Kaplan-Meyer actuarial method.

RESULTS

During the study period, 105 patients ≥70 years of age (mean 75 ± 4) with acute MI were referred for direct PTCA (Table I). Ten elderly patients with previous bypass surgery reported in an earlier series were not included.[9] The mean duration of chest pain was 5.2 ± 3.5 hours; 56 patients (53%) presented within 4 hours from time of pain onset. Twelve patients were in cardiogenic shock, 4 of whom were receiving cardiopulmonary resuscitation on the way to the cardiac catheterization laboratory.

Findings at catheterization and outcomes from percutaneous transluminal coronary angioplasty (Figure 1): Multivessel disease as defined by a stenosis of ≥70% in ≥2 major epicardial coronary arteries was present in 67% of the patients. The infarct-related artery was determined by electrocardiographic location and the angiographic appearance of the suspected vessel (e.g., presence of thrombus, subtotal occlusion with poor anterograde flow, total occlusion). The overall success rate in dilating the infarct vessel to <40% residual stenosis was 91% (Table II). The location and patency of the vessel did not significantly alter the primary success rate. One patient with a subtotal distal left main occlusion was referred for bypass surgery after successful PTCA.

Hospital mortality and morbidity: Only 1 patient died during the acute procedure. The overall hospital mortality rate was 18%. Six of the 19 hospital deaths (32%) occurred in patients who presented in cardiogenic shock. Multivariate analysis of the variables time, location of infarction, gender, infarct-related artery, number of vessels diseased, success of direct PTCA and cardiogenic shock at presentation showed that 3-vessel disease and shock were the most predictive variables for in-hospital mortality.

No stroke or intracranial or gastrointestinal hemorrhages occurred in this group of patients. Two patients had significant complications at the vascular access site; 1 required surgical repair of the femoral artery and the other required blood transfusion.

Repeat catheterization: Recurrent chest pain with electrocardiographic changes occurred in 14 of the 95 patients who had successful direct PTCA intially. Reocclusion of the infarct vessel was found in 10 of these patients, whereas the other 4 had a patent infarct-related vessel and no anatomic basis for ischemia. Six patients underwent successful repeat dilation, and 4 were sent for bypass surgery.

Of 72 patients with a stable hospital course, 48 (67%) consented to repeat coronary angiography. Silent reocclusion of the infarct-related artery was found in 3 patients, 14 had restenosis defined as luminal narrowing >50%, and 32 had continued wide patency of the infarct-related artery. During the predischarge procedure, 14 patients underwent successful PTCA of additional noninfarct artery–related stenosis. The remaining 33 patients who did not have repeat angiography before discharge were judged to be stable and free of ongoing ischemia based on noninvasive testing and clinical assessment (Figure 1).

Changes in ventricular function: Paired ventriculograms were available in 51 patients (48 pairs from patients with a stable hospital course and a predischarge study and 3 pairs from patients who had chest pain in the hospital and a patent infarct-related artery). The global ejection fraction improved from 54 ± 13 to 61 ± 15% (p <0.001). Regional wall motion improved significantly in the segments supplied by the infarct vessel in 62% of the patients.

Long-term follow-up: The 1- and 5-year mortality rates, including in-hospital deaths for the entire group were 73 and 67%, respectively (Figure 2). However, the major contributor to this high rate was in-hospital mortality. Patients presenting initially in cardiogenic shock had an in-hospital mortality rate of 50%, but only 1 of the 6 patients discharged alive died within the first 12 months. Patients with 3-vessel coronary artery disease had an in-hospital mortality rate of 46%, but only 9% died during the first 6 months after hospital discharge.

Repeat PTCA was performed in 12 patients during the first 6 months after hospital discharge for restenosis and other significant stenoses not dilated during the acute hospitalization. Myocardial infarction occurred in 5 patients during this period.

TABLE II Comparison of Clinical Characteristics and Outcomes of Young and Elderly Patients

	<70 years	≥70 years	p
No. of patients	438	105	
Age (mean yrs)	56 ± 9	75 ± 4	<0.001
Men	332 (76%)	58 (55%)	<0.001
Infarction location			
Anterior	179 (41%)	52 (50%)	
Inferior	259 (59%)	53 (50%)	0.13
Diseased vessels			
1	210 (48%)	35 (33%)	
2	145 (33%)	46 (44%)	
3	83 (19%)	24 (23%)	0.02
Shock	23 (5%)	12 (11%)	0.15
Primary success	414 (95%)	95 (91%)	0.18
In-hospital death	23 (5%)	19 (18%)	<0.001
6-month survival	93%	77%	
12-month survival	92%	73%	
Urgent bypass surgery	8 (2%)	3 (3%)	0.42
Vascular complications	6 (1%)	2 (2%)	0.63

Comparison with younger patients: These results were compared to 438 patients aged <70 years without previous bypass surgery who were treated similarly during the same time period (Table II). The most striking differences between the 2 groups were that the older patient was more likely to present in cardiogenic shock and have multivessel coronary artery disease. The in-hospital and 6-month mortality rates were 3 times higher for the elderly. There was no difference in the technical success rate of direct PTCA, nor was there a higher incidence of vascular complications.

DISCUSSION

Advanced age is a powerful predictor of mortality during acute MI, with reported in-hospital mortality rates ranging from 20 to 33%.[1-3] Because thrombolytic agents cause an especially high incidence of hemorrhagic complications in this group, the elderly have usually

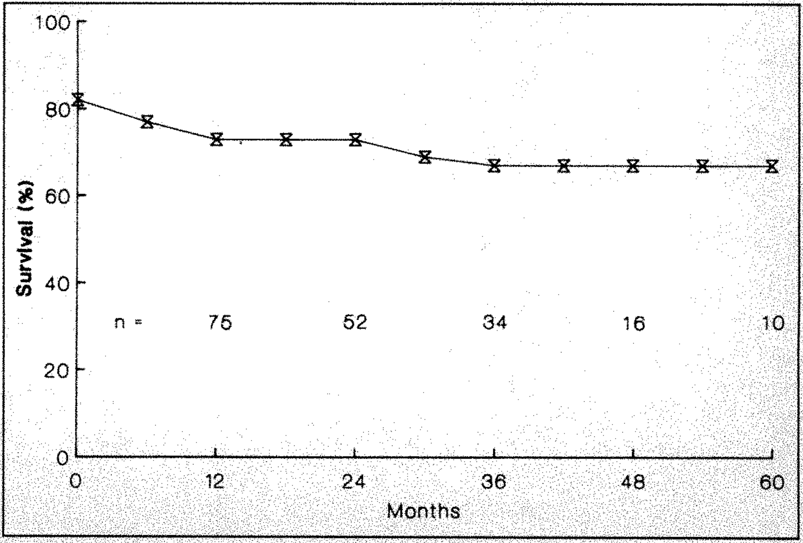

FIGURE 2. Survival curve of the entire group including in-hospital deaths. n = the number of patients available for follow-up at each time point.

been excluded from most thrombolytic trials. Two large studies using streptokinase for acute MI reported mortality rates ranging from 16 to 29% in the elderly.[10,11] Furthermore, despite development of more clot selective and potent thrombolytic agents, the reperfusion rate using these agents alone plateau at 75%.[12]

Technical success of direct percutaneous transluminal coronary angioplasty: We have shown that direct PTCA may be performed safely and with a high primary success rate in the elderly (91%). This reperfusion rate is comparable to our previously published overall experience with direct PTCA (94%) and other reports using direct PTCA as the primary method of reperfusion in acute MI.[7-9,13] In a series of 35 elderly patients described by Holland et al,[14] the primary success rate was 74% with a correspondingly higher hospital mortality. We attribute our higher success rate to operator experience (each operator has performed more than 500 elective PTCAs) and the laboratory support staff, which is well trained for this procedure (more than 14,000 elective PTCAs and 1,000 direct infarct PTCAs have been performed by the laboratory overall).

Vascular and bleeding complications: Bleeding complications have been a major cause of hospital morbidity related to acute interventions, especially when preceded by thrombolytic agents. The incidence of major bleeding complications, including intracranial hemorrhage and need for transfusion, is especially high in the elderly.[5,6] Significant bleeding from vascular access sites is enhanced by catheterization and PTCA soon after administration of thrombolytic therapy.[15-18] Heparin and aspirin have been routinely used with direct PTCA in several series and the incidence of hemorrhage is low. The 2% incidence of vascular complications resulting from intervention in this group of elderly patients is comparable to lower risk groups previously reported.[7,9,13]

Recurrent ischemic symptoms: Although successful direct PTCA results in a widely patent infarct-related artery, the early reocclusion rate is relatively high: 11% in this series, when compared with elective PTCA, <5%.[19] Nevertheless, the 10% early reocclusion rate is relatively low when compared with the 15 to 25% early reocclusion rate when thrombolytic therapy is given alone.[20,21] In most cases reocclusion can be successfully redilated and patency maintained with judicious use of heparin.

Myocardial salvage: As in many other series using direct PTCA for acute MI intervention, we have observed improvement in ejection fraction and regional wall motion in our patients.[7,9] In part, this consistent improvement in ejection fraction may be attributable to the rarity of hemorrhagic infarction in patients treated with PTCA alone. In a postmortem series, Waller et al[23] observed hemorrhagic infarction in all 14 patients when thrombolytic therapy was used, whereas no myocardial hemorrhage was seen in patients treated with PTCA alone (5 of 5 patients). Mathey et al[23] reported a case of a patient with anterior and inferior infarctions separated by time, 1 treated with thrombolytic therapy and the other by PTCA, documenting hemorrhage only in the infarction treated with thrombolytic therapy. Myocardial hemorrhages have been observed to extend into areas of noninfarcted myocardium with potential to further impair ventricular function.[24] Although the clinicopathologic correlation of myocardial hemorrhage and ejection fraction must be further studied, these pathologic reports give a reasonable anatomic basis for repeated studies showing measurable myocardial salvage with direct PTCA.

Mortality: Historically, the in-hospital mortality rate for the elderly ranges from 20 to 33%.[1,2] Our overall mortality rate of 18% included 12 patients in cardiogenic shock. Because of the accessibility of the catheterization laboratory to patients in the emergency room with evolving acute MI, patients who might otherwise die despite resuscitative efforts in the emergency room were included. Indeed, 3 of the 4 patients receiving cardiopulmonary resuscitation on the way to the catheterization laboratory died. The 18% mortality rate in our patients is equivalent to the 18% mortality rate in the treatment group (aspirin and streptokinase) of elderly patients reported by the International Study of Infarct Survival-2 investigators. The mortality rate of elderly patients receiving a placebo was 24% in this large series.[11]

The investigators of the Western Washington streptokinase trial were the first to link vessel patency to long-term survival after acute MI.[25] Patients with larger infarct territories, as in anterior infarctions, benefit the greatest from a patent infarct vessel. We interpret the relatively low 1-year mortality of 27% in the study group to the high primary success rate of direct PTCA. For instance, the Italian Group for the Study of Streptokinase in Myocardial Infarction investigators reported 1-year mortality rates of 43 to 46% in their elderly control group.[26] Since the elderly are already a high-risk group, they have the most to gain from infarct intervention. Hence, the large difference in long-term survival between the study group and historical controls is not surprising.

Restenosis: The in-hospital restenosis rate was 29% in patients who had predischarge angiography. Because patients with markedly positive exercise test results were more likely to undergo a repeat study, this restenosis rate is probably an overestimate of its true incidence. This rate is similar to the 31% incidence reported by Rothbaum et al.[7] All restenoses were successfully redilated.

Among the 48 patients who underwent elective predischarge angiography, 3 patients had silent reocclusion of the infarct vessel. Analysis of patient demographics, infarct vessel, infarct location, hospital mortality, and long-term mortality and morbidity between the patients who underwent predischarge angiography and those who did not, failed to reveal any differences between the groups.

Limitations: This report summarizes the consecutive experience in a large group of elderly patients treated with direct PTCA for acute MI. Although these results may be compared with results from recent thrombolytic trials, firm conclusions regarding the relative merits of these 2 modalities cannot be made because of the retrospective and nonrandomized design of this study. Furthermore, since predischarge studies were available in only 67% of patients with a stable hospital course, the restenosis and silent reocclusion rates can only be estimates of the true incidence of these events.

Clinical implications: Although the elderly with acute MI are a high-risk group, the technical success rates for direct PTCA are comparable to that experienced in younger patients. Improvement in left ventricular function can be demonstrated and mortality is significantly improved when compared with untreated elderly patients in recent thrombolytic trials and historical controls. Furthermore, only 2 of 105 patients had significant vascular complications resulting from direct PTCA and there were no strokes. Direct PTCA, when applied by experienced operators in a facility geared toward its application as primary therapy, is an effective and safe method to salvage myocardium and improve mortality in this high-risk group.

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Circadian Distribution of the Characteristics of Ischemic Episodes in Patients with Stable Coronary Artery Disease

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To determine the circadian distribution of episodes of myocardial ischemia, studies were performed in 111 patients with chronic stable angina pectoris, positive exercise test results and angiographically proven coronary artery disease. During 24 hours of ambulatory electrocardiographic monitoring, 101 symptomatic and 298 asymptomatic ischemic episodes (ST-segment depression >1 mm, duration >1 minute) were observed. The number of ischemic episodes and the cumulative duration of ischemia showed a circadian variation with the highest values between 8 and 10 A.M. and between 4 and 5 P.M. associated with a similar circadian variation of heart rate. Mean duration of ischemic episodes, maximal amplitude of ST-segment depression during ischemic episodes and increase in heart rate before the onset of ischemic episodes showed no significant circadian variation. Heart rate at the onset of ischemic episodes and maximal heart rate during ischemic episodes were lower between midnight and A.M. than during other times of the day.

The morning and afternoon increase in ischemic activity is not paralleled by changes reflecting a decrease in myocardial oxygen supply during these periods (heart rate at onset of ischemia, heart rate increase before onset of ischemia), but is paralleled by a similiar circadian variation of heart rate. The circadian variation in ischemic activity is predominantly based on a comparable variation in myocardial oxygen requirements.

(Am J Cardiol 1990;66:668–672)

Several clinical manifestations of coronary artery disease show a characteristic circadian rhythm: Acute myocardial infarction,[1] sudden cardiac death,[2,3] and ventricular arrhythmias[4-6] occur more frequently between 6 and 12 A.M. than during other hours of the day. Ambulatory monitoring of electrocardiographic ST-segment changes has revealed a similar circadian variation in patients with stable angina. The highest incidence of ischemic episodes was observed during the morning hours between 6 and 12 A.M.[7-10] This morning increase in ischemic activity is discussed as one possible explanation for the circadian distribution of the clinical events. However, the diurnal variation of other important characteristics of the ischemic episodes, such as duration and amplitude of ST-segment changes, heart rate changes before and during ischemia, has not been determined previously.[7-10] Therefore, we examined the circadian variation of several characteristics of ischemic episodes in patients with stable angina, positive results on exercise testing, and angiographically proven coronary artery disease.

METHODS

Patients: One hundred eleven patients (97 men and 14 women, mean age ± standard deviation 57 ± 9 years [range 32 to 81]) were included in this prospective study. The following selection criteria were fulfilled: (1) chronic stable angina pectoris for >3 months, (2) maximal exercise stress testing (according to age and gender) with >1 mm horizontal or downsloping ST-segment depression, (3) angiographic evidence of >70% stenosis in ≥1 major coronary artery or >50% stenosis of the left main coronary artery, (4) normal ST-segments in the standard electrocardiogram at rest and during postural changes, and (5) >1 ischemic episode during ambulatory monitoring over 24 hours. Patients receiving digitalis or antiarrhythmic drug therapy and patients with left ventricular hypertrophy, cardiomyopathy, rheumatic valve disease, aortocoronary bypass grafts, prior coronary angioplasty or conduction abnormalities on the electrocardiogram were excluded from this study.

Cardiac catheterization: All patients underwent right- and left-sided cardiac catheterization with coronary and left ventricular angiography. The degree of coronary artery stenosis was estimated from several standard and half-axial projections. Stenoses with a reduction of >70% of the luminal diameter (or of 50% for stenoses of the left main coronary artery) were consid-

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ered clinically relevant (visual analysis). By this definition, 38 patients had 1-, 34 had 2- and 30 had 3-vessel disease. A significant stenosis of the left main coronary artery was present in 9 patients.

Ambulatory electrocardiographic monitoring: Ambulatory monitoring of the electrocardiogram was performed using a 2-channel, direct-recording system ("Tracker," Reynolds Medical). The bipolar electrodes were localized at the upper right sternal border and precordially in the CM_3 and CM_5 position. The site of the electrodes was occasionally modified in order to simulate the lead with the strongest ST-segment deviation during the exercise test. Stability of the ST-segment was confirmed with the patient in a supine, upright, left and right lateral position. The tapes were analyzed visually and computerized at 60 times real speed using the "Pathfinder III" (Reynolds Medical). Episodes were classified as "ischemic" in the presence of >1 mm ST-segment deviation 80 ms after the J point, lasting for 60 seconds and separated by 60 seconds from another ischemic episode. During ambulatory monitoring the patients were not restricted in their physical activities and were asked to write a protocol concerning their anginal symptoms. The patients received no antiischemic therapy except for short-acting nitroglycerin during anginal attacks. Ten of the 111 patients had been treated by β blockers before; this therapy has been discontinued ≥ 3 days before the recording period.

The mean, maximal and minimal heart rates were measured for each hour interval for each individual patient. For the ischemic episodes the following parameters were determined: (1) time of onset of ischemia (at the beginning of 1 mm ST-segment deviation), (2) duration of the ischemic episode, (3) maximal heart rate during the episode, (4) maximal amplitude of ST-segment changes, (5) heart rate at the onset of ischemia (at the beginning of 1 mm ST-segment deviation), and (6) increase in heart rate during the last 5 minutes before the onset of ST-segment depression.

Statistics: The individual values of mean, maximal and minimal heart rates during each hour of the day were averaged; thus, these heart rates for each hour were determined for the whole study group. The total number and cumulative duration of ischemic episodes were determined for each hour of the day. The characteristics of the ischemic episodes were expressed as mean values for each hour interval of the day.

The periodic pattern of the occurrence of ischemic episodes was computed by a multiple logistic regression model (MLR = maximum likelihood method). The diurnal distribution of the characteristics of the ischemic episodes and of heart rate was tested by a multiple linear regression model. In both models the regression equation was fitted using linear combinations of cyclic functions (sin(nx), cos(nx), with $n = 1 \ldots 4$, and $0 < X < 2$). Model goodness of fit was evaluated by chi-square statistics for the multiple linear regression and a p value <0.05 was considered significant.[11] For the logistic regression the goodness of fit chi-square was used to test that the model fits adequately; a low p value means that the predicted values do not fit the data.

RESULTS

Circadian distribution of the number and cumulative duration of ischemic episodes (Figure 1): Ambulatory monitoring of the electrocardiogram revealed 399 ischemic episodes with ST-segment depression; transient ST-segment elevation was not observed. There were 101 (25%) symptomatic and 298 (75%) asymptomatic ischemic episodes. The circadian distribution of the number of ischemic episodes is shown in Figure 1. The incidence of ischemic episodes was highest during the morning hours between 8 and 10 A.M.; in addition, another smaller peak was observed during the afternoon between 4 and 5 P.M. During evening and night, the frequency of

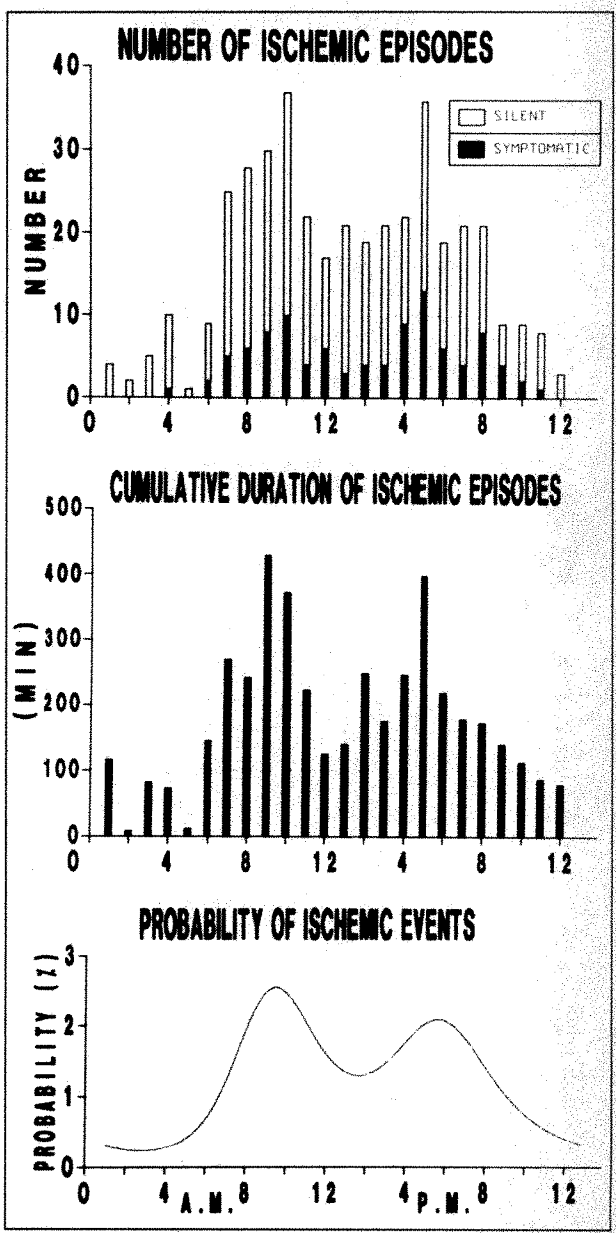

FIGURE 1. Circadian variation of ischemic episodes in patients with stable coronary artery disease. *Top,* number of ischemic episodes; *middle,* cumulative duration of ischemic episodes; *bottom,* probability of the occurrence of ischemic episodes during time intervals of 5 minutes (goodness of fit = 0.326).

ischemic episodes was low. The cumulative duration of ischemic episodes was 4,301 minutes for the whole group; this parameter showed a circadian distribution comparable to the number of ischemic episodes, with a first peak in the morning and another smaller peak in the afternoon (Figure 1). The periodic pattern of the occurrence of an ischemic episode was computed by a multiple logistic regression model; in Figure 1, the probability of the occurrence of an ischemic episode during time intervals of 5 minutes is listed (goodness of fit = 0.326).

Circadian distribution of the characteristics of ischemic episodes (duration and amplitude of ST-segment depression, heart rate before and during ischemic episodes) (Figures 2 and 3): The mean duration of the ischemic episodes was 11 ± 12 minutes (median 7 minutes). The circadian distribution of this parameter is shown in Figure 2. The mean duration of the episodes showed a wide scatter during different hours of the day. The maximal amplitude of ST-segment depression during ischemic episodes averaged 2.1 ± 0.8 mm with a median of 2.0 mm; this parameter also varied randomly throughout the day (Figure 2). Duration of ischemic episodes and maximal amplitude of ST-segment depression during ischemic episodes showed no significant circadian variation.

Heart rate before and during the ischemic episodes is shown in Figure 3. The increase in heart rate before onset of ischemia was 13 ± 13 beats/min (median 12

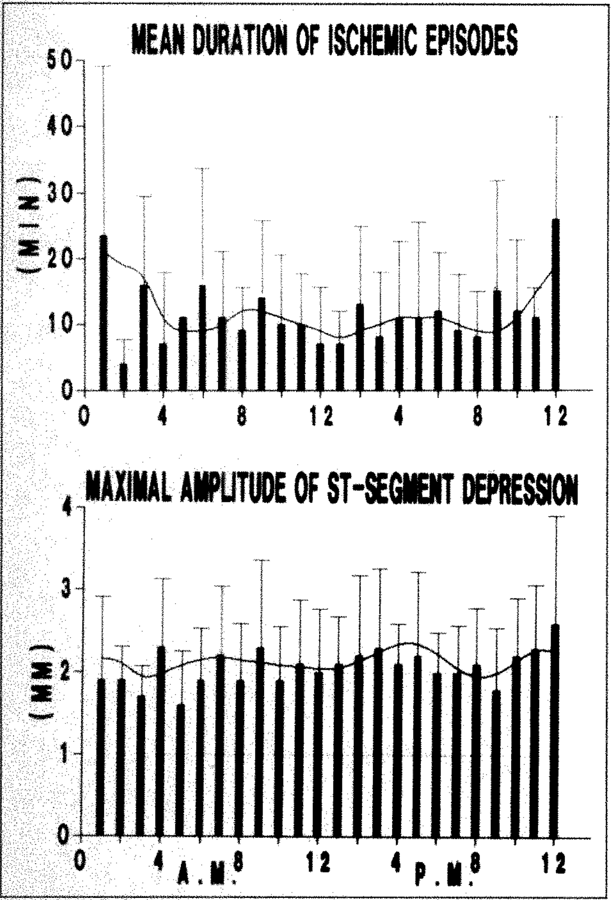

FIGURE 2. Circadian distribution of characteristics of ischemic episodes. *Top*, duration of the ischemic episodes; *bottom*, maximal amplitude of ST-segment depression. Values are expressed as mean ± 1 standard deviation. Multiple regression analysis *(wavy line)* revealed no significant circadian variation for both parameters (difference not significant).

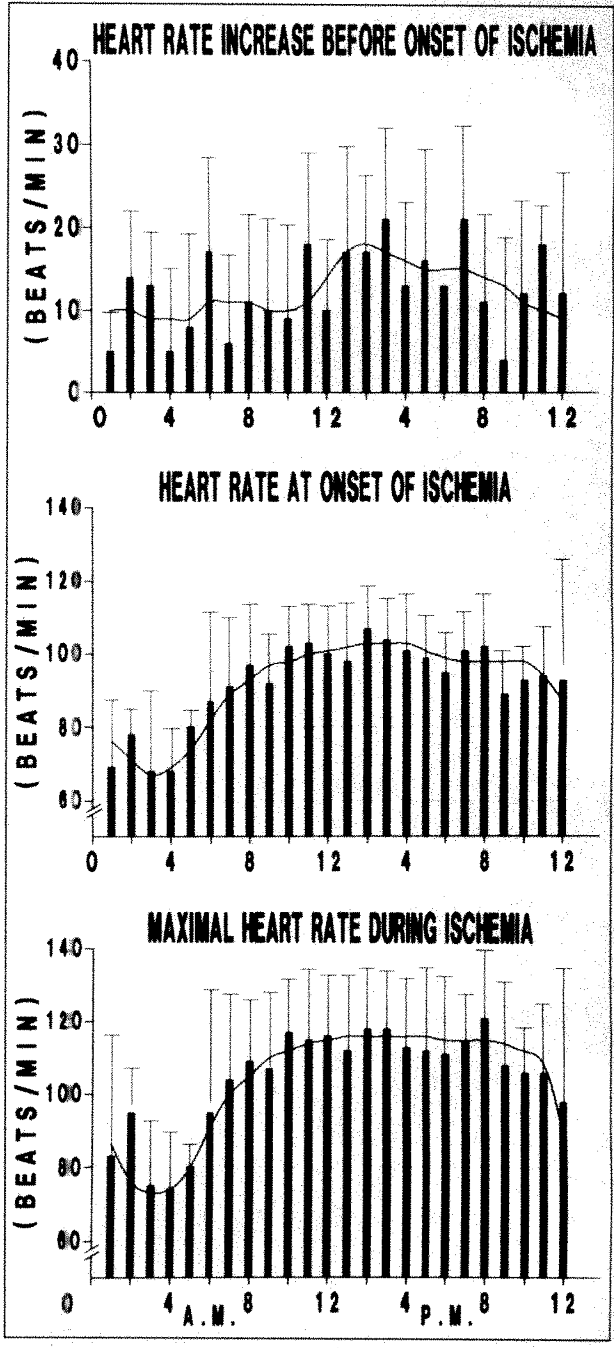

FIGURE 3. Circadian distribution of characteristics of ischemic episodes. *Top*, increase in heart rate before onset of ischemic episodes; *middle*, heart rate at onset of ST-depression; *bottom*, maximal heart rate during ischemic episodes. Values are expressed as mean ± 1 standard deviation. Multiple regression analysis *(wavy line)* revealed a significant circadian variation for heart rate at the onset of ischemic episodes and for maximal heart rate during ischemic episodes ($p < 0.001$). Heart rate increase before onset of ischemic episodes showed no significant circadian variation (difference not significant).

beats/min). This parameter also varied between different hours, but showed no significant circadian rhythm. Heart rate at the onset of ischemic episodes was 99 ± 17 beats/min (median 100 beats/min); in episodes occurring between midnight and 6 A.M. this parameter was lower compared with the episodes during the remaining hours of the day. The maximal heart rate during ischemic episodes averaged 111 ± 21 beats/min (median 115 beats/min) (Figure 3). This parameter was also lower for episodes occurring between midnight and 6 A.M. Heart rate at the onset of ischemic episodes and maximal heart rate during ischemic episodes showed a significant circadian variation ($p < 0.001$) determined by a multiple linear regression model.

Circadian distribution of heart rate (Figure 4): Maximal, mean and minimal values of heart rate were determined for every hour of the day for each patient. The circadian distribution of these parameters is shown in Figure 4. Heart rates increased between 8 and 10 A.M. and had another peak between 4 and 5 P.M. In contrast, the heart rate decreased after 8 P.M. and had lowest values between midnight and 5 A.M. Multiple linear regression analysis revealed a distinct circadian rhythm for these parameters ($p < 0.001$). The diurnal pattern of heart rate was comparable to the circadian variation of the number and cumulative duration of the ischemic episodes as described elsewhere in this manuscript.

DISCUSSION

The increased incidence of acute myocardial infarction,[1,12] sudden cardiac death[2,3] and ventricular arrhythmias[4-6] in the morning hours indicates that this period of the day is a fragile phase in patients with coronary artery disease. Comparable circadian distributions are known for plasma levels of catecholamines[13] and cortisol,[14] for arterial blood pressure,[15] heart rate[16] and platelet aggregability,[17,18] and for fibrinolytic activity,[19] explaining in part the increased incidence of cardiac events during the morning hours. The increase in ischemic activity during the morning hours has been discussed as an additional explanation for the circadian rhythm of these clinical events.[7] Nevertheless, previous studies have only analyzed the diurnal distribution of the number of ischemic episodes and the cumulative duration of ischemia during ambulatory monitoring.[7-10]

The objective of the present study was to determine the circadian distribution of other characteristics of ischemic episodes. Our study confirmed that ischemic episodes occur more frequently in the morning and in the afternoon hours compared with other periods of the day. A similar diurnal variation was observed for heart rate measured continuously in all patients. Mean duration of the ischemic episodes, maximal amplitude of ST depression and increase in heart rate before ischemic episodes showed no significant circadian variation; heart rate at the onset of ischemic episodes and maximal heart rate during ischemic episodes were lower between midnight and 6 A.M. compared with the remaining hours of the day.

If changes in myocardial oxygen supply during different times of the day were the cause for the circadian variation of ischemic activity, this would be reflected by changes in the threshold for the ischemic episodes. In this case, heart rate at the onset of ischemic episodes and the heart rate increase before ischemia would be lower during the morning and the afternoon hours compared with other hours of the day. Our study showed that these parameters were not lower during the morning and afternoon hours. In contrast, heart rate at onset of ischemia was higher during the periods with an increased ischemic activity, indicating an even higher ischemic threshold. These findings show that increased ischemic activity must primarily be based on parallel changes in myocardial oxygen demand during the morning as well as during the late afternoon.

Although ischemic activity in patients with stable angina pectoris is known to be highest during the active hours of the day,[7-10] the primary reduction in myocardial oxygen supply in Prinzmetal's variant angina causes an inverse diurnal distribution.[8,20] In patients

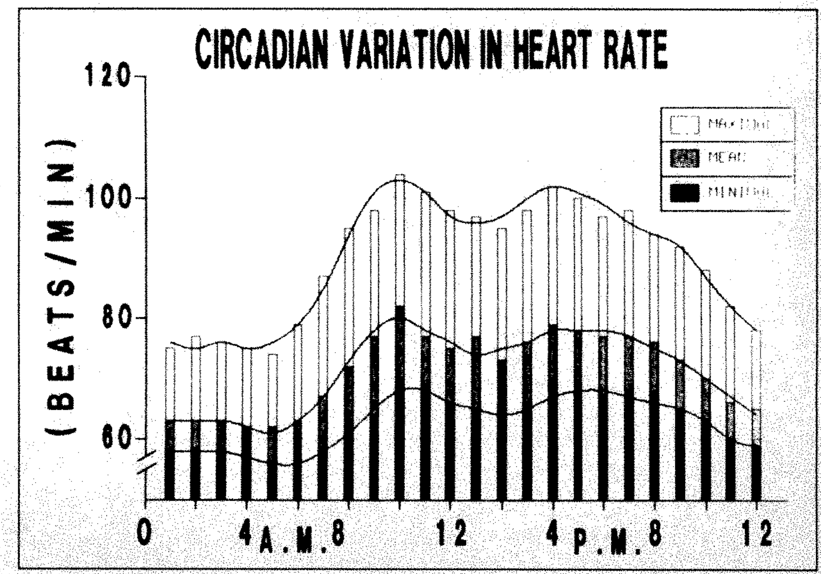

FIGURE 4. Circadian variation of heart rate. Values for maximal, mean and minimal heart rates. Multiple regression analysis *(wavy lines)* revealed a significant circadian rhythm for these parameters ($p < 0.001$).

with "mixed" angina, ST-segment depression reflecting subendocardial ischemia occurs more frequently during the daytime and ST-segment elevation representing transmural ischemia predominantly occurs during the night.[21] This different pattern in ischemic activity also supports the finding that the morning increase in ischemic activity in stable angina pectoris is predominantly based on changes of myocardial oxygen requirements.

Recently, a close coupling between the circadian variation in heart rate and ambulatory ischemia has been described by Lambert et al.[22] This coupling was greatly altered by β-adrenergic blockade. Other therapeutic interventions with β-blocking agents have also shown that the morning peak in ischemic activity can effectively be reduced by decreasing myocardial demand.[9,23,24] Improvement in myocardial supply by calcium channel blockers also reduces number and duration of ischemic episodes. However, it does not significantly change the morning increase in ischemic activity.[9] These observations confirm that changes in myocardial oxygen demand and supply contribute to the occurrence of ischemic episodes during daily life. Nevertheless, the different effects of these drugs on the circadian variation of myocardial ischemia also confirms that changes in myocardial oxygen requirements are more important for the morning increase in ischemic activity.

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Long-Term Follow-Up of Postmyocardial Infarction Patients with Ventricular Tachycardia or Ventricular Fibrillation Treated with Amiodarone

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Amiodarone in a low dose (200 mg/day) was administered alone or in combination with other type I antiarrhythmic drugs as a first-line agent in 33 patients with ventricular tachycardia (VT) (n = 24) or ventricular fibrillation (VF) (n = 9) secondary to coronary artery disease with healed myocardial infarction. There were 30 men and 3 women (mean age 69 ± 9 years). Left ventricular ejection fraction ranged from 16 to 45% (mean 29 ± 8). Therapy was guided by the results of electrophysiologic studies without the use of a control study (without drugs). Predischarge electrophysiologic studies revealed inducible sustained VT in 8 patients (24%), nonsustained VT in 7 and noninducible VT in 18 patients. Mean follow-up time was 27 ± 7 months. Eleven patients (33%) died, 5 suddenly (15%) and 6 from nonarrhythmic causes. Five patients (15%) had nonfatal recurrences of VT. Life-table analysis showed that arrhythmic recurrences or fatalities (VT or sudden death) were related to the results of the predischarge electrophysiologic studies and not to the baseline arrhythmia (VT or VF). Toxicity from amiodarone was uncommon and no patient discontinued taking the drug.

(Am J Cardiol 1990;66:673–678)

Amiodarone administered in relatively high doses has been considered an effective therapeutic agent for the treatment of ventricular tachyarrhythmias. It has previously been used for patients with "drug resistant" ventricular tachycardia (VT) or ventricular fibrillation (VF) due to its high incidence of adverse effects. This report presents our experience with amiodarone given in low doses and as the first choice antiarrhythmic agent in a selected population with healed myocardial infarction presenting with sustained VT or VF.

METHODS

Inclusion criteria: Since 1982, patients admitted to our hospital with an episode of sustained VT or VF were considered for amiodarone therapy. For this study, only patients with coronary artery disease and proven healed myocardial infarction (>2 months old) were included. In addition, the admission episode of VT or VF had to be unrelated to acute myocardial infarction or ischemia, electrolyte imbalance, drug toxicity or long QT syndrome. Acute myocardial infarction was ruled out because of the lack of development of new Q waves and normal creatine kinase-MB fraction. Acute ischemia could not be completely ruled out (e.g., silent ischemia); however, patients with a history of unstable angina or those in whom dynamic ST-T changes developed after the VT-VF episode were excluded.

Protocol: After the conversion to sinus rhythm, therapy was begun with oral amiodarone, 1.2 g/day, for 10 days. After this loading dose, an electrophysiologic study was performed to assess drug response (see later). In cases in which the response was considered adequate, amiodarone was tapered down within 2 to 4 weeks to the maintenance dose (200 mg/day). In cases in which the response was considered inadequate, a repeat study was performed using drug combinations (amiodarone and type I antiarrhythmic agents). Left ventricular ejection fraction was calculated by left ventricular radionuclear angiography. Coronary angiography was performed only in selected cases. No patient underwent coronary artery bypass surgery.

Electrophysiologic study: As stated, the electrophysiologic study was performed at the end of the amiodarone loading period; therefore, no control study (without drugs) was performed. The study consisted of the introduction of single and double ventricular extrastimuli coupled to ventricular-driven cycle lengths of 600 and

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TABLE I Characteristics of the Study Population

Pt.	Age (yr) & Sex	MI Location	EF%	Antiarrhyth.	EPS	FU (mon)	Recurrence	Outcome
				Monomorphic Sustained Ventricular Tachycardia				
1	69 M	A + I	20	AM	0	52	—	Alive
2	83 M	A + I	23	AM + Q	VT	6	VT	Died (CHF)
3	75 F	I	38	AM + M	NSVT	44	—	Died (hip surgery)
4	64 M	I	33	AM + Q	NSVT	66	—	Alive
5	64 M	A	27	AM	0	25	—	Died (CHF)
6	73 M	I	42	AM	VT	51	—	Died (MI)
7	48 M	A	25	AM + M	NSVT	56	—	Alive
8	75 M	I	30	AM	VT	3	VT	Died (CHF)
9	71 M	A	32	AM	0	48	—	Alive
10	74 M	A	30	AM	0	40	VT	Alive
11	79 M	I	39	AM	0	18	—	Alive
12	69 M	A	20	AM	0	21	—	Alive
13	74 M	A	30	AM	0	24	—	Alive
14	64 F	A	30	AM	0	30	—	Alive
15	71 M	I	40	AM	NSVT	22	—	Alive
16	73 F	A	29	AM + Q	VT	40	VT	Alive
17	65 M	A	19	AM	0	30	—	Alive
18	61 M	A	18	AM	0	43	—	Alive
19	66 M	A	38	AM	0	40	—	Alive
20	79 M	A	38	AM	0	18	—	Alive
21	59 M	A + I	22	AM	VT	3	VT-VF	Died (sudden)
22	79 M	A	25	AM	0	3	—	Alive
23	64 M	I	35	AM + Q	NSVT	17	—	Alive
24	50 M	I	38	AM	NSVT	5	—	Alive
				Ventricular Fibrillation Group				
25	75 M	A	16	AM	0	30	—	Alive
26	58 M	I	42	AM	0	44	—	Alive
27	60 M	I	38	AM	VT	13	VT	Died (surgery MVR)
28	66 M	A	15	AM	VT	15	VT-VF	Died (sudden)
29	78 M	I	45	AM	0	21	—	Alive
30	77 M	A	26	AM + Q	0	27	—	Died (sudden)
31	72 M	I	25	AM	NSVT	13	VT-VF	Died (sudden)
32	57 M	A	27	AM	0	18	—	Alive
33	79 M	I	22	AM	VT	1	VT-VF	Died (sudden)

A = anterior; Antiarrhyth. = antiarrhythmic drugs; AM = amiodarone; CHF = congestive heart failure; EF = ejection fraction; EPS = electrophysiologic study; FU = follow-up; I = inferior; M = mexiletine; MI = myocardial infarction; MVR = mitral valve replacement; NSVT = nonsustained ventricular tachycardia; Q = quinidine; VT = ventricular tachycardia; VF = ventricular fibrillation.

500 ms, respectively. No S_4 or rapid ventricular pacing was attempted. Ventricular extrastimulation was performed at 2 right ventricular sites, the apex and outflow tract, and using a stimulation strength of twice diastolic threshold. Induced VT was considered sustained when it lasted ≥ 30 seconds; it was considered nonsustained when it lasted <30 seconds. VT was considered noninducible when a maximum of 5 ventricular responses was elicited. An adequate response for the amiodarone study was considered when VT was either nonsustained or noninducible. In patients with sustained VT, a repeat study was performed using drug combinations when the induced VT (with amiodarone alone) was either very fast (rate >200/min) or it was hemodynamically poorly tolerated. Patients were also discharged if the induced VT was still sustained but with a relatively slow rate and with no evidence of major hemodynamic compromise.

Follow-up: After discharge, patients were seen at 3-month intervals. Holter studies were obtained at 4- to 6-month intervals. Liver and thyroid function tests were obtained at each visit. Chest x-rays were obtained every 6 months.

Statistical analysis: Life-table analysis was performed using the method of Kaplan and Meier, with comparison between survival curves analyzed by the method of Breslow and Mantel-Cox. The chi-square analysis and Fischer's exact test were also used for analysis of the significance of the results of predischarge electrophysiologic studies with regard to arrhythmia recurrence and differences in mortality and arrhythmia recurrences between groups. A p value <0.05 was considered significant. For the purpose of statistical analysis, induction of nonsustained VT (<30 seconds' duration) was considered as noninducible VT.

RESULTS

The clinical and arrhythmic characteristics of the 33 patients included in this study are listed in Tables I and II. With the exception of 1 patient who developed VT 6 months after his infarction, the age of the last infarction in the remaining patients was >1 year.

Results of electrophysiologic study: The predischarge electrophysiologic study revealed inducible sustained monomorphic VT in 8 patients (24%) (5 from the VT group and 3 from the VF group). Nonsustained VT was induced in 7 patients. It was monomorphic in 6 (all of whom belonged to the VT group) and it was polymorphic in 1 patient (VF group). No inducible arrhythmias were demonstrated in 18 patients. Thirteen of these patients belonged to the VT group and 5 to the VF group.

Follow-up (Table II): The follow-up period ranged from 1 to 66 months (mean 27 ± 17). During the follow-up period, 11 patients died (33%), 5 suddenly (15%), 5 from nonsudden cardiac causes (15%) and 1 patient from a noncardiac cause (3%). Five patients (15%) had a nonfatal recurrence of VT. Figure 1 shows the group's life-table analysis according to total mortality and arrhythmic recurrences (VT and sudden death).

Correlation between ventricular tachycardia inducibility at predischarge electrophysiologic studies and outcome: Of the 8 patients with inducible sustained VT, 7 had clinical arrhythmic recurrences, namely, VT or sudden death, and 1 remained asymptomatic. In contrast, of the 25 patients with either noninducible or nonsustained VT, only 3 had a clinical recurrence, $p < 0.001$. The results of the electrophysiologic studies with regard to prediction of outcome yielded a sensitivity of 70%, a specificity of 95.6%, a positive predictive value of 87.5% and a negative predictive value of 88%.

TABLE II Clinical Characteristics and Follow-Up

	All Pts. (n = 33)	VT Group (n = 24)	p Value	VF Group (n = 9)
Age (years)	60 ± 9	69 ± 9	NS	69 ± 9
Men	30	17	—	13
Ejection fraction (%)	29 ± 8	29 ± 7	NS	30 ± 10
Follow-up (months)	27 ± 17	29 ± 19	NS	20 ± 12
Total mortality	11 (33%)	6 (25%)	NS	5 (55%)
Sudden death	5 (15%)	1 (4%)	<0.005	4 (44%)
Nonfatal VT	5 (15%)	4 (16%)	NS	1 (11%)

NS = not significant; VF = ventricular fibrillation; VT = ventricular tachycardia.

Ventricular tachycardia versus ventricular fibrillation groups: Table II depicts the characteristics and outcome according to the presenting clinical arrhythmia. Both groups were similar with respect to age, left ventricular ejection fraction and length of follow-up. The total mortality and incidence of sudden death were higher in the VF group. In contrast, the incidence of recurrent nonfatal VT was higher in the VT group. In the VT group (24 patients), clinical recurrences of VT or sudden death were observed in 4 of the 5 patients with inducible VT, whereas recurrences were observed in only 1 of the 19 patients with either noninducible or nonsustained VT. In the VF group (9 patients), clinical recurrences were observed in all 3 of the 3 patients with inducible VT, whereas clinical recurrences were seen in 2 of the 6 patients with noninducible or nonsustained

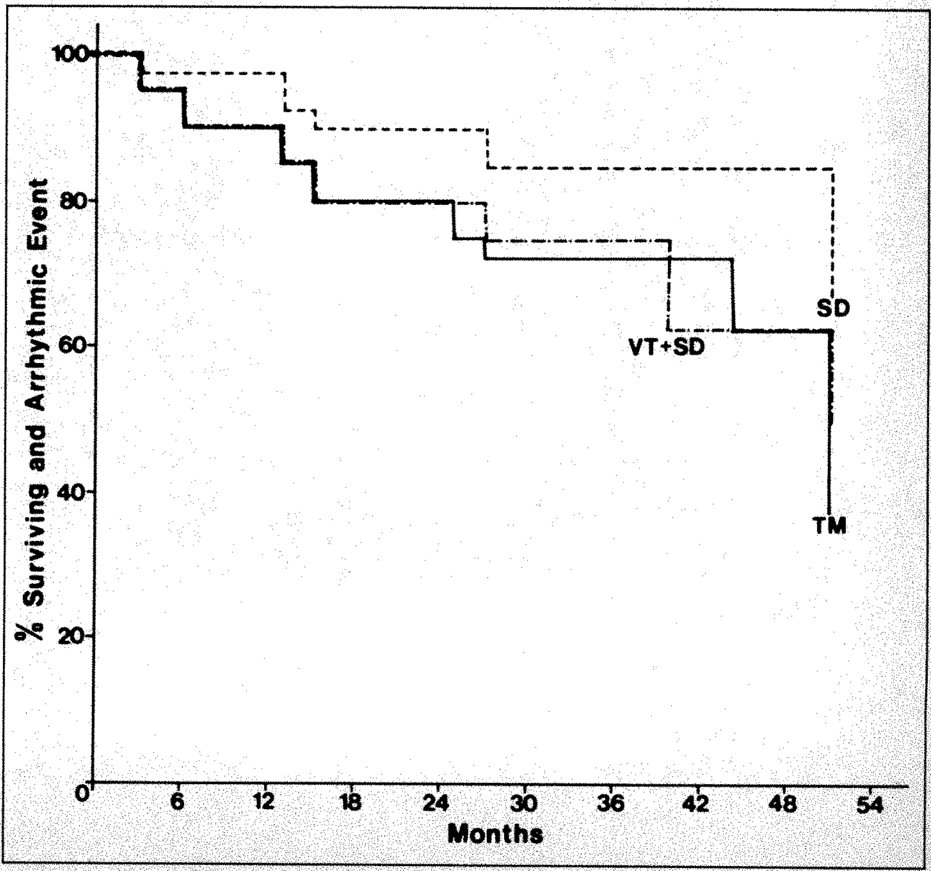

FIGURE 1. Life-table analysis showing the percentage of patients surviving from all causes of death and free of any arrhythmic event (sustained ventricular tachycardia [VT] and sudden death [SD]). TM = total mortality.

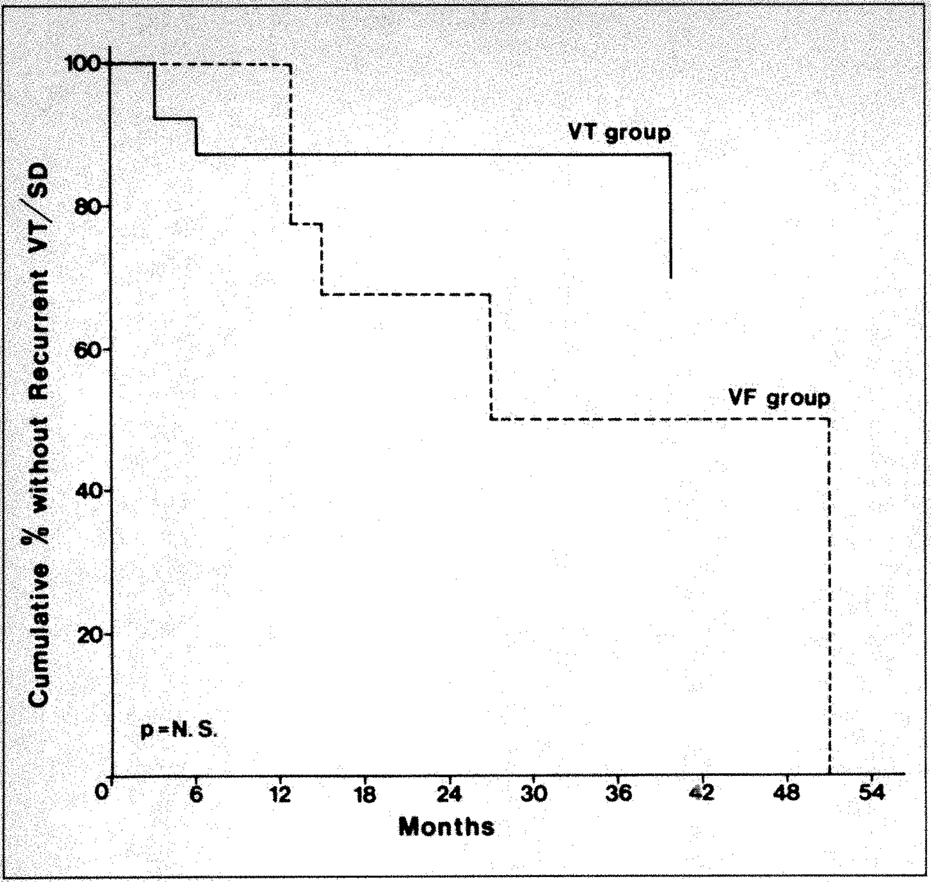

FIGURE 2. Life-table analysis showing the cumulative percent without recurrent ventricular tachycardia (VT) or sudden death (SD) based on the presenting clinical arrhythmia, VT versus ventricular fibrillation (VF). N.S. = not significant.

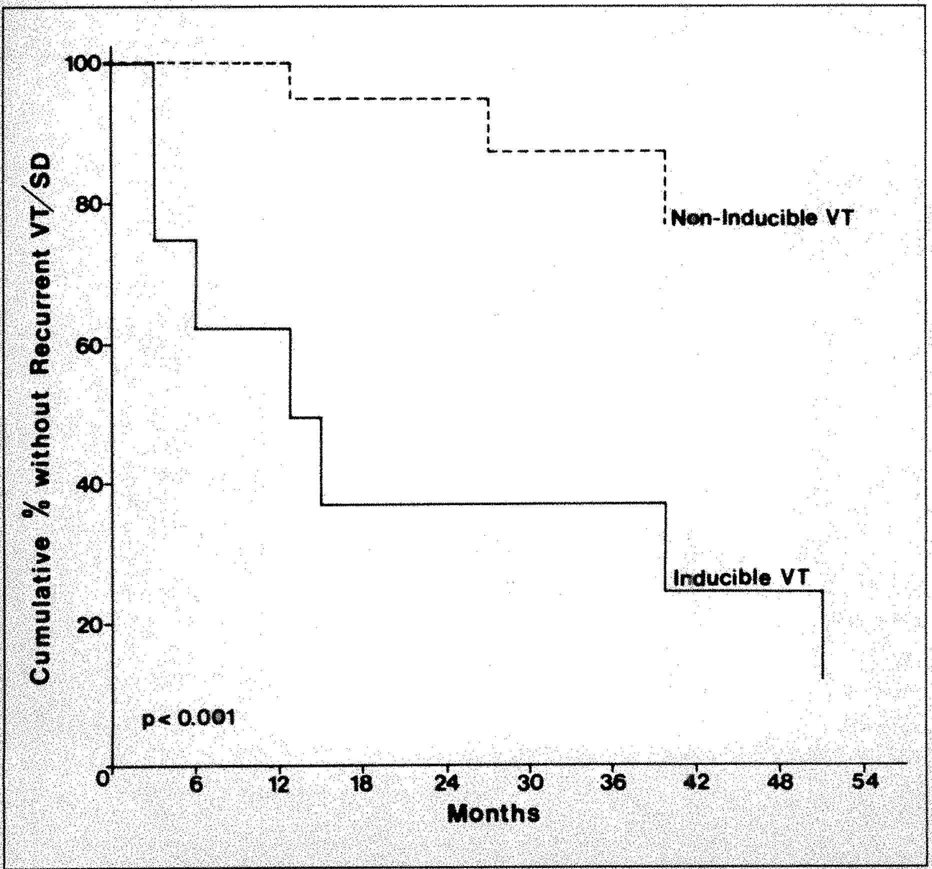

FIGURE 3. Life-table analysis showing the cumulative percent without recurrent ventricular tachycardia (VT) or sudden death (SD) based on the results of the predischarge electrophysiologic study.

VT. One of the latter 2 patients with clinical recurrences had reproducibly inducible nonsustained polymorphic VT and died suddenly after 13 months of therapy, and the remaining one had noninducible VT and died suddenly 27 months later. For the VT group, the predischarge electrophysiologic studies had a sensitivity of 80%, specificity of 95%, positive predictive value of 80% and a negative predictive value of 95%. For the VF group, these values were 60, 100, 100 and 66.6%, respectively. Figures 2 and 3 show the life-table analysis of both groups based on the presenting clinical arrhythmia and the results of the predischarge electrophysiologic study. In Figure 2 the specific outcome of the patients (VT or sudden death) is analyzed with the presenting clinical arrhythmia (VT or VF). No statistical differences between groups were observed. In Figure 3, the same specific outcome (VT or sudden death) was analyzed against the result of the predischarge electrophysiologic study (inducible versus noninducible or nonsustained VT). In this case, a strong statistical significance ($p < 0.001$) was found. Figure 4 shows the life-table analysis of the groups' specific outcome (VT or sudden death) comparing both groups (VT versus VF) with their predischarge studies. A statistically significant difference ($p < 0.002$) was found between the 4 groups, with both groups without inducible VT showing a better outcome.

Adverse effects: Permanent pacemakers had to be installed in 2 patients, in 1 for severe symptomatic sinus bradycardia and in the second patient, with preexisting atrial fibrillation, for increasing atrioventricular block. In 1 patient both photosensitivity and marked asymptomatic bluish decoloration of the face were noted. No thyroid, liver or pulmonary toxicity was noted. In no patient was the dose of amiodarone reduced or the drug discontinued.

DISCUSSION

An abundance of reports have been published during the past decade regarding the efficacy and long-term results of amiodarone therapy in patients with sustained VT or VF. These reports have recently been summarized by Greene.[1] Almost all studies had certain features in common; they tested amiodarone in patients already resistant to previous conventional or investigational antiarrhythmic drugs and they used a moderate to high dose of amiodarone (>400 mg/day). In this study we evaluated patients with rather advanced ischemic heart disease and proven myocardial infarction (mean ejection fraction 29 ± 8%). In contrast to previous studies, amiodarone was given as the first-line agent and low maintenance dose (200 mg/day) was administered to all patients. After a follow-up period of 27 ± 17 months, we observed a 33% mortality (Table II, Figure 1). This was due to nonsudden cardiac causes (mainly from heart failure) in half of these patients. With regard to arrhythmia, 70% of the patients remained symptom free, 5 (15%) died suddenly and 5 (15%) had

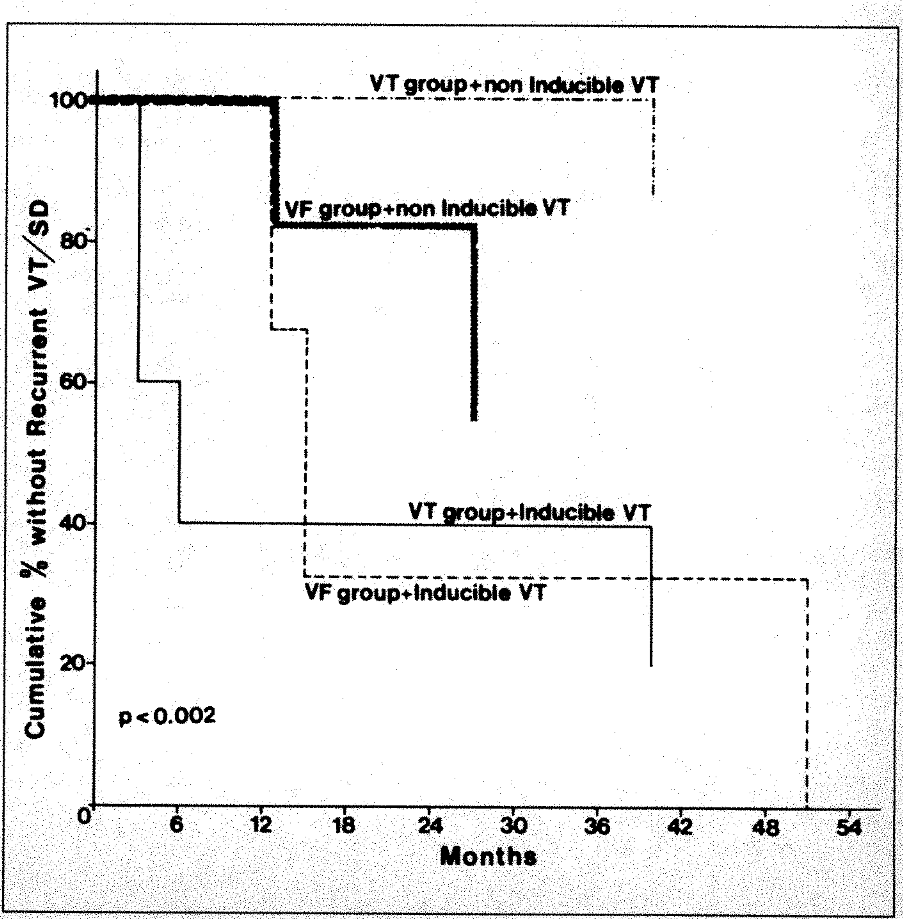

FIGURE 4. Life-table analysis showing the cumulative percent without recurrent ventricular tachycardia (VT) or sudden death (SD) based on both the clinical arrhythmia (ventricular tachycardia [VT] versus ventricular fibrillation [VF]) and the results of the predischarge electrophysiologic study.

nonfatal recurrence of VT. The actuarial probability of freedom from any arrhythmia (VT or VF) at 24 and 48 months was 80 and 62.5%, respectively, whereas for sudden death alone it was 90 and 85%. The results we observed differ from some previous studies[1-3] but are in agreement with 2 large recent studies.[4,5]

Role of electrophysiologic studies: The role of electrophysiologic studies in predicting arrhythmic outcome for patients treated with amiodarone has been greatly debated. The initial general consensus was negative[6-8]; however, subsequent reports have shown a good predictive value.[4,9,10] Patients with either noninducible or nonsustained VT are at low risk for arrhythmic recurrence, whereas patients with inducible sustained VT or VF have a higher incidence of arrhythmic recurrence or sudden death.[4,9,10] One major limitation in this study is the lack of a control study and the use of the clinical arrhythmia as the control VT-VF. Therefore, we cannot be sure that all the patients had inducible sustained VT in the control state. However, our population was strictly selected using patients with healed myocardial infarction and decreased ejection fraction. It has been well recognized that in this group, the incidence of laboratory induction of VT was very high in patients with monomorphic sustained VT.[11-13] In the group with VF, the incidence of laboratory induction of VT-VF was lower than in the group with sustained VT.[11-13] However, in our VF group all patients were men and had healed myocardial infarction, the 2 variables that were found to be the strongest predictors of arrhythmia inducibility in survivors of VF.[14] In contrast, there are possible advantages of not performing a control study such as shorter hospitalization time and therefore reduced costs, avoiding an invasive and aggressive procedure and decreasing the incidence of electrical cardioversions. The incidence of cardioversions in VT studies ranges from 21 to 52%.[15-18] The rate of induced VT is 1 of the major determinants of success or failure of pacing cardioversion. The VT rate induced without drugs is faster than with drugs; therefore, antiarrhythmic drugs improve the chances of pacing cardioversion by slowing VT.[15-18] The VF group had a much poorer prognosis than the VT group, with a sudden death rate of 44%. However, life-table analysis showed that the clinical outcome was related to the results of the electrophysiologic study and not to the type of clinical arrhythmia (VT or VF) (Figures 2 to 4).

Toxicity: One of the major limitations of amiodarone treatment is its high incidence of adverse effects.[1] This toxicity has been partly related to the dosage and serum levels.[1] Amiodarone had to be discontinued because of adverse effects in approximately 14% of patients during the first year of therapy, with a subsequent discontinuation rate of 6%/year.[5] We observed only 2 types of toxicity: (1) cardiac, manifested by the need for permanent pacing; and (2) dermatologic, manifested by photosensitivity and skin discoloration. No pulmonary or thyroid complications were noted. There was no need to reduce or discontinue amiodarone in any patient.

Clinical implications: Amiodarone, alone or in combination with type I agents, when given in low dosage (200 mg/day) and with therapy guided by the results of electrophysiologic studies is an effective first-line antiarrhythmic therapy, with a low incidence of adverse effects, for patients with healed myocardial infarction presenting with sustained VT (80% success). For the group with VF the results are disappointing. However, the results of the electrophysiologic study may help to decide if further interventions, such as an implantable defibrillator, are indicated.

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Comparison of Nicorandil and Atenolol in Stable Angina Pectoris

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and Edward B. Raftery, MD

The efficacy of nicorandil was compared with atenolol in 37 patients with chronic stable angina using a randomized, placebo-controlled, parallel study design. After a single-blind placebo phase, patients were randomized to receive nicorandil or atenolol using a double-dummy technique. Patients took nicorandil 10 mg twice daily or atenolol 50 mg once daily for the first 3 weeks, and if no adverse effects were encountered they took nicorandil 20 mg twice daily or atenolol 100 mg once daily, for the final 3-week phase. Treadmill exercise tests were performed at the end of each treatment phase immediately before and 2 hours after the morning dose of medication. Groups were demographically similar. Placebo exercise times were 7.06 (0.60) minutes (mean ± standard error of the mean) in the nicorandil group and 6.81 (0.47) minutes in the atenolol group. After 6 weeks, improvements in exercise time were before dosing: +1.47 (0.40) minutes with nicorandil ($p < 0.005$) and +1.33 (0.29) minutes with atenolol ($p < 0.001$). Improvements after therapy was administered were +2.45 (0.41) minutes with nicorandil ($p < 0.001$) and +2.37 (0.43) minutes with atenolol ($p < 0.0001$). Whereas, the predose peak exercise double product (heart rate × systolic blood pressure mm Hg/100) was reduced with atenolol (−43.6 units; $p < 0.001$), an increase (+7.56 units; difference not significant) was noted with nicorandil. One patient taking atenolol and 5 taking nicorandil developed persistent headaches. One subject with severe 3-vessel coronary artery disease had fatal myocardial infarction within 3 days of starting nicorandil, 10 mg twice daily. Nicorandil and atenolol produce comparable improvement in exercise time in patients with stable angina but the former does not reduce myocardial oxygen demand. This new agent may be beneficial in patients with angina in whom β blockers are contraindicated, although headache may be a problem in a significant minority of patients.

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Nicorandil is a new antianginal drug that has been shown in animals and humans to have potent vasodilating and antispasmodic properties which may be relatively selective to the coronary arteries.[1-3] The compound enhances potassium transport across cellular membranes[4,5] and also contains a nitrate moiety. Despite the fact that nicorandil is a nitrate ester, its cardiovascular action differs from nitroglycerin in several respects. In particular, it has little effect on cardiac output, arterial blood pressure and pulse pressure.[2] Early studies indicate that tolerance is less likely than with standard nitrate preparations.[5,6] An increase in both cyclic guanosine monophosphate[7] and released prostacyclin from vascular microsomes[8] have also been reported, which suggests other mechanisms of coronary vasodilation. The half-life of 6 to 8 hours permits twice-daily dosage, and total-daily dosages between 10 and 40 mg have been effective in patients with chronic stable angina.[9-11] To assess the clinical efficacy and the anti-ischemic properties of nicorandil, it was compared with the proven cardioselective β blocker atenolol[12-14] in patients with chronic stable angina.

METHODS

Patients: Thirty-seven patients (35 men, 2 women) with angiographically proven coronary artery disease (≥1 vessel with >70% luminal diameter stenosis) and stable anginal symptoms for a minimum of 6 months were studied. Strict inclusion criteria were applied that required the development of reproducible angina during treadmill exercise, associated with a minimum of 1 mm ST-segment depression measured 80 ms after the J point. Patients with recent myocardial infarction (<3 months) labile ST/T-wave syndrome, hypertension (>170/100 mm Hg) or those with angina due to valvular disease were excluded as were women of childbearing age. All cardiovascular drugs (except sublingual nitroglycerin) were withdrawn 14 days before trial entry.

Trial design: The trial consisted of 3 phases (Figure 1). An initial, single-blind placebo assessment was performed in all subjects. This comprised a baseline exercise test and 1 week of placebo (2 capsules twice daily in identical form to the later active medication) followed by 2 further tests: 1 before the trial morning dose of placebo and one 2 hours later. Patients exhibiting >20% variability in exercise time between these 3 tests were excluded. Those fulfilling the entry criteria were randomized into 2 groups to receive nicorandil (10 mg twice daily for 3 weeks followed by 20 mg twice daily for 3 weeks) or atenolol (50 mg/day for 3 weeks fol-

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TABLE I Demographic and Anthropomorphic Details of the Two Patient Groups

	Nicorandil (n = 19)	Atenolol (n = 18)
Age (years)	61 (range 51–70)	61 (range 44–70)
Male/female	19/0	16/2
Previous MI	7/19	7/18
Smoker	1 current 12 ex	3 current 12 ex
Height (cm) mean ± SD	173 (7.0)	170 (8.1)
Weight (kg) mean ± SD	77 (9.6)	72 (6.8)
Duration of symptoms (mo)	79 (range 6–260)	41 (range 6–180)

ex = ex smoker; MI = myocardial infarction; SD = standard deviation.

lowed by 100 mg/day for 3 weeks). Tests were performed at the end of each phase before and 2 hours after the morning dose.

Exercise testing: Exercise testing was performed at the same time each morning (0900 to 1100 hours) in a temperature-controlled laboratory according to American Heart Association regulations.[15] Patients were asked not to smoke or to take sublingual nitroglycerin on the morning of their tests. Maximum symptom-limited graded treadmill exercise testing was performed on a motorized treadmill linked to an on-line computer analysis system (Case I-Marquette Electronics Inc.) using continuous monitoring of bipolar leads CM5 and CC5. In each patient the lead showing the greatest ST change was identified and used in all subsequent tests to determine the time to 1 mm of ST depression. A modified Chung protocol was used as previously described.[16] The computer provided digital measurement of the ST-segment level to an accuracy of 0.1 mm measured 80 ms after the J point or one-eighth of the RR interval, whichever was shorter. Systolic blood pressure was recorded by sphygmomanometer every 3 minutes during exercise and the results entered into the computer.

Subjective improvement in symptoms was monitored by patient diary cards.

Statistical analysis: Treadmill test times to peak exercise, time to angina and time to 1 mm ST depression were analyzed by survival techniques with log rank statistics to compare treatments. Heart rates and blood pressures were compared using t tests and differences from day 8 were used.

The study was approved by the hospital ethics committee and all patients gave written consent.

RESULTS

Thirty patients completed the trial. One patient with severe 3-vessel coronary artery disease had fatal myocardial infarction on the third day of active treatment with nicorandil. An additional 6 patients withdrew because of persistent severe headaches (5 nicorandil, 1 atenolol). In those who completed the study, all had their doses increased to the maximum without significant adverse effects, except 1 patient taking atenolol who developed a resting bradycardia <50 beats/minute with 50 mg. The demographic details of the 2 groups are listed in Table I.

Exercise time: Changes in exercise time, time to angina and time to 1 mm ST depression are shown in Figure 2. Predose exercise time increased from 7.06 (0.60) (mean ± standard error of the mean) minutes with placebo to 8.53 (0.74) minutes with nicorandil 20 mg (difference 1.47 [0.40] minutes [$p < 0.005$]). With atenolol 100 mg, the increase was from 6.81 (0.47) to 8.14 (0.57) minutes (difference 1.33 [0.29] minutes [$p < 0.001$]). Postdose exercise time increased from 7.32 (0.59) to 9.77 (0.65) minutes with nicorandil (difference 2.45 [0.41] minutes [$p < 0.0001$]) and from 7.12 (0.46) to 9.49 (0.62) minutes with atenolol (difference 2.37 [0.43] minutes [$p < 0.0001$]). Time to 1 mm ST depression and time to angina increased both before and after administration of nicorandil and atenolol when compared with placebo times (Figure 1). There were no statistical differences between the magnitude of improvement in the 2 treatment groups.

Heart rate and blood pressure: Differences in the change of heart rate and blood pressure between the 2 drug treatments are shown in Figure 3. Compared with placebo, predose resting heart rate decreased 1.42 (3.08) beats/min with nicorandil and 19.72 (2.77)

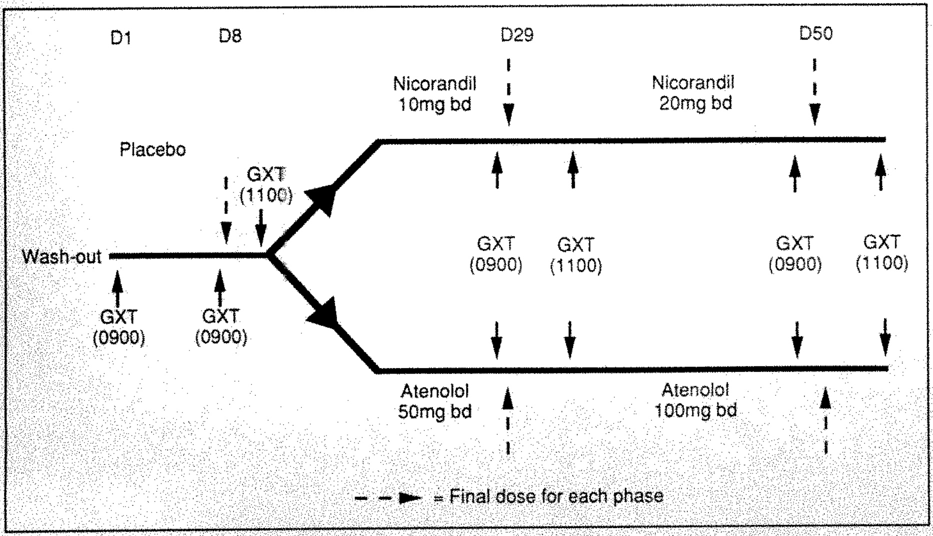

FIGURE 1. Trial design showing parallel study after single-blind placebo phase. D = day; GXT = graded exercise testing.

beats/min with atenolol—a highly significant difference between treatments ($p < 0.0001$). Peak exercise heart rate increased 3.33 (2.25) beats/min with nicorandil and decreased 16.56 (4.08) beats/min with atenolol ($p < 0.0001$). Predose resting systolic blood pressure decreased 3.36 (4.67) mm Hg with nicorandil and 6.89 (3.62) mm Hg with atenolol (difference not significant). Relative to placebo, maximum systolic blood pressure increased 1.67 (5.23) mm Hg with nicorandil but decreased 17.50 (4.23) mm Hg with atenolol ($p < 0.001$). The predose peak exercise double product (maximum heart rate × systolic blood pressure mm Hg/100) increased by 7.56 units with nicorandil compared with a significant decrease of 43.6 units with atenolol ($p < 0.0001$).

The incidence of severe headache was 5 of 19 in the nicorandil group, and an additional 6 patients had mild, transient headaches. The frequency of anginal attacks decreased with both drugs, from 4 to 2/week with nicorandil and from 5 to 2/week with atenolol. Glyceryl trinitate consumption decreased from 4 to 1/week with nicorandil and from 2 to 1/week with atenolol.

DISCUSSION

Despite the availability of numerous drugs to treat patients with chronic stable angina, the negative inotropic and chronotropic effects of β blockers and some calcium antagonists and the problem of tolerance with chronic nitrate therapy justifies the search for new effective agents. Nicorandil is a new drug that augments potassium transport across cell membranes,[6] causing vasodilatation, and also contains a nitrate moiety. The drug has been shown in animal and human studies to possess potent vasodilating properties.[1–3] The efficacy of nicorandil was compared with the β blocker atenolol which has proven value in chronic stable angina.[12–14] The statistical power of the study was low and proving equivalence in the efficacy of the 2 treatments on the basis of our results was considered unlikely. However, the demographic similarity of the 2 patient groups enabled comparisons of the mode of action of the 2 drugs to be made.

The principal aim was to examine the relative benefits of nicorandil (20 mg twice daily) with a commonly prescribed dose of atenolol (100 mg/day). However, a lower initial dose with an increase after 3 weeks of therapy was included in the protocol to minimize the incidence of adverse effects in the initial treatment phase. Exercise testing was performed at the same time of day (0900 to 1100 hours) for each patient and only those with reproducible angina were included. The double-dummy medication format ensured that both patient and investigator were blinded during the active treatment phases. By these means, observed changes were highly likely to be due to drug effect rather than spurious influences.

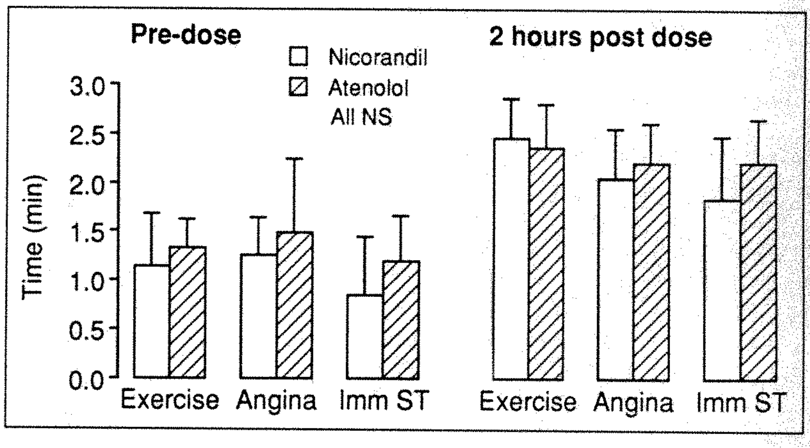

FIGURE 2. Mean ± standard error of the mean *(bars)* changes in exercise time, time to angina and time to 1 mm ST depression, before and 2 hours after nicorandil 20 mg or atenolol 100 mg. Changes with respect to end placebo (day 8) are shown. No statistically significant (NS) difference between the 2 drug treatments was found.

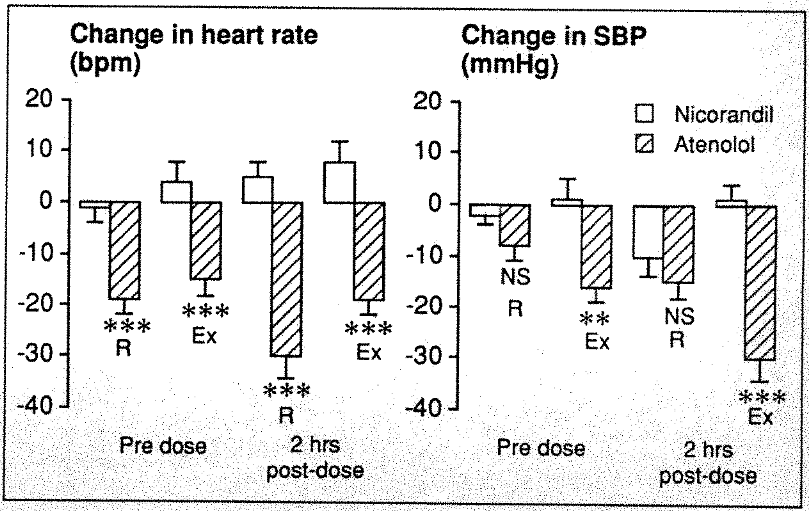

FIGURE 3. Mean ± standard error of the mean *(bars)* changes in rest (R) and exercise (Ex) heart rate and systolic blood pressure (SBP). Changes with respect to end placebo (day 8) are shown. Statistical differences between the 2 treatment groups are shown. **p = <0.001; ***p = <0.0001; NS = not significant.

Both drugs produced comparable improvement in exercise time before and 2 hours after the final morning dosage, and the more objective index of ischemia (time to 1 mm ST depression) also showed significant and comparable improvement. The increase in exercise time with nicorandil, 20 mg, was similar to that described by Hayata et al[9] in patients who exercised 30 minutes after receiving an identical oral dose. However, in our study patients were assessed at the end of a 6-week treatment period, which suggests that an attenuation of antiischemic effect may not be present with nicorandil. The improvement in exercise time in the atenolol group was also comparable to those previously described in similar patients. The significant and comparable improvement in exercise time before the morning dose of medication with both drugs indicates that nicorandil, 20 mg twice daily, is as effective as atenolol, 100 mg once daily, in providing 24-hour antiischemic benefit to patients with stable angina.

However, the mechanism of action of the 2 drugs, inferred by the hemodynamic changes, were different. Atenolol improved exercise time by reducing the exercise heart rate and systolic blood pressure, thus reducing myocardial oxygen demand at all work loads. Nicorandil did not reduce the predose peak exercise double product, and peak oxygen demand was therefore not altered by the drug. Resting blood pressure was reduced, suggesting a peripheral vasodilatory action. The improvement in exercise capacity with nicorandil was thus mediated through a reduction in afterload, and the small increase in peak exercise rate pressure product may reflect a degree of coronary vasodilation with subsequent alteration in coronary reserve.

Severe headaches were encountered by approximately one-third of the patients taking nicorandil and caused 5 subjects to discontinue. In all these cases headaches remained without diminution during treatment, implying a sustained vasodilating effect. The sustained hemodynamic changes in those who were assessed after 6 weeks of treatment with nicorandil also suggest that the well-described phenomenon of tachyphylaxis seen with many nitrate compounds[17,18] may not occur with nicorandil.

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Effects of Nitroglycerin at Therapeutic Doses on Platelet Aggregation In Unstable Angina Pectoris and Acute Myocardial Infarction

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The platelet aggregation response to adenosine diphosphate (ADP) and to thrombin was quantified in 10 patients, 5 with unstable angina pectoris and 5 with acute myocardial infarction, before, during and after a 45-minute infusion of nitroglycerin. An impedance aggregometer allowing rapid bedside studies in whole blood was used. The reproducibility of the methods was documented to be within 10%. Doses of nitroglycerin were titrated for a 10 mm Hg decrease in mean arterial blood pressure with mean doses being 1.2 ± 0.2 (standard error of the mean) μg/kg/min. Nitroglycerin decreased the area under the aggregation curve induced by ADP from 43 ± 3.6 to 30 ± 6.3 cm^2 ($p = 0.007$) and by thrombin from 8.9 ± 1.7 to 4.1 ± 0.9 cm^2 ($p = 0.003$). Peak responses to ADP were decreased from 13.3 ± 1 to 9.1 ± 1.7 ohms ($p = 0.005$) and to thrombin from 9.3 ± 2 to 5.0 ± 1.2 ohms ($p = 0.003$). All patients had ≥50% inhibition with 1 agent or the other and the inhibition was >50% with each of the 2 aggregating agents in 6 patients. Analyses performed on blood withdrawn 15 minutes after the discontinuation of nitroglycerin showed a return to baseline before nitroglycerin results. When analyses were delayed and performed on blood preserved at room temperature for 30 minutes, no effect of nitroglycerin could be detected. Thus, bedside platelet aggregation studies document a significant and reversible effect of nitroglycerin at therapeutic doses on platelet function.

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Nitroglycerin has played an important role in medical practice for more than a century.[1] Its usefulness has stimulated continuous research on its mechanisms of action, which have improved understanding of the pathophysiology of angina pectoris. Nitroglycerin decreases myocardial oxygen consumption by its peripheral vasodilating effects.[2] The drug also increases myocardial oxygen supply through dilatation of the large coronary arteries.[3] Other possible beneficial effects include an increase in coronary collateral flow[4] and favorable redistribution of regional flow.[5]

Nitroglycerin is also widely used in unstable angina and acute myocardial infarction,[6,7] clinical syndromes in which platelet aggregation and thrombus formation play a major role.[8] Attempts to document an effect of nitroglycerin on these processes have generally failed[9–12] or yielded controversial results.[13] Although in vitro[14] and in vivo experimental studies[15] have shown that nitroglycerin could inhibit platelet aggregation, this effect has not been confirmed in man at therapeutic doses.[9,16,17] The aim of this study was to reassess the effects of nitroglycerin on platelet aggregation in patients with acute ischemic syndromes. For this purpose, we used a new method allowing rapid, bedside determination of platelet aggregation in whole blood.[18]

METHODS

Population: Ten patients (8 men, 2 women) with documented coronary artery disease were studied. Mean age was 58 years (range 38 to 76). The patients were selected from the coronary care unit population of our institution; 5 had unstable angina and were studied shortly after admission; the other 5 had acute myocardial infarction and were studied 5 to 7 days after the acute phase. Concomitant medications included a calcium antagonist in 5 patients, captopril in 1 and digoxin in 1. Exclusion criteria were use of nitrates, aspirin, nonsteroidal antiinflammatory agents, heparin and fibrinolytic agents in the 10 days before the study, difficult venous puncture access or refusal by the patient to participate in the study.

Perfusion of nitroglycerin: Tests were carried out in the fasting state, without recent tobacco use and with a previously installed intravenous line with dextrose 5% in water running at a minimum rate. The blood pressure and heart rate were measured every 5 minutes for 15 minutes or until stable baseline values were recorded. Nitroglycerin infusion (30 mg in 250 cc of dextrose 5% in water) was started at 10 cc/hr and increased by in-

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crements of 10 cc/hr every 5 minutes until a 10% decrease in mean arterial blood pressure was seen. Dose titration was stopped before reaching this end point in 3 patients because of side effects. The solution of nitroglycerin was prepared by the pharmacist of the hospital just before the study without addition of any preservatives; specifically, no ethanol was added. The infusion of nitroglycerin was terminated after 45 minutes. Venous blood samplings for the determination of platelet aggregation were obtained by the same well-trained person using a 19-gauge butterfly needle inserted in an antecubital vein with minimal trauma and stasis. Different puncture sites were used for each sampling. Blood samples were obtained just before the start and before the end of the 45-minute perfusion of nitroglycerin and again in 6 patients, 15 minutes after discontinuation of the drug.

Platelet aggregation studies: Platelet aggregation was tested at 37°C on whole blood diluted 1:1 in sterile

TABLE I Changes in Heart Rate and Blood Pressure

Age (yrs)	Sex	Dose of Nitroglycerin ($\mu g/kg/min$)	HR (beats/min) Before	HR (beats/min) During	Mean BP (mm Hg) Before	Mean BP (mm Hg) During
Unstable Angina						
76	M	1.69	64	83	103	93
68	M	1.54*	55	64	93	87
63	M	0.57	63	61	83	70
41	F	0.74*	74	84	73	70
49	F	1.90*	60	61	92	94
Myocardial Infarction						
61	M	1.23	73	66	90	70
38	M	0.86	80	86	80	70
53	M	1.82	80	86	93	80
62	M	1.11	71	80	77	70
68	M	0.44	70	76	86	77
Mean ± SEM		1.19 ± 0.2	69 ± 3	75 ± 3	87 ± 3	78 ± 3
p			<0.02		<0.001	

* Titration stopped because of side effects.
SEM = standard error of the mean.

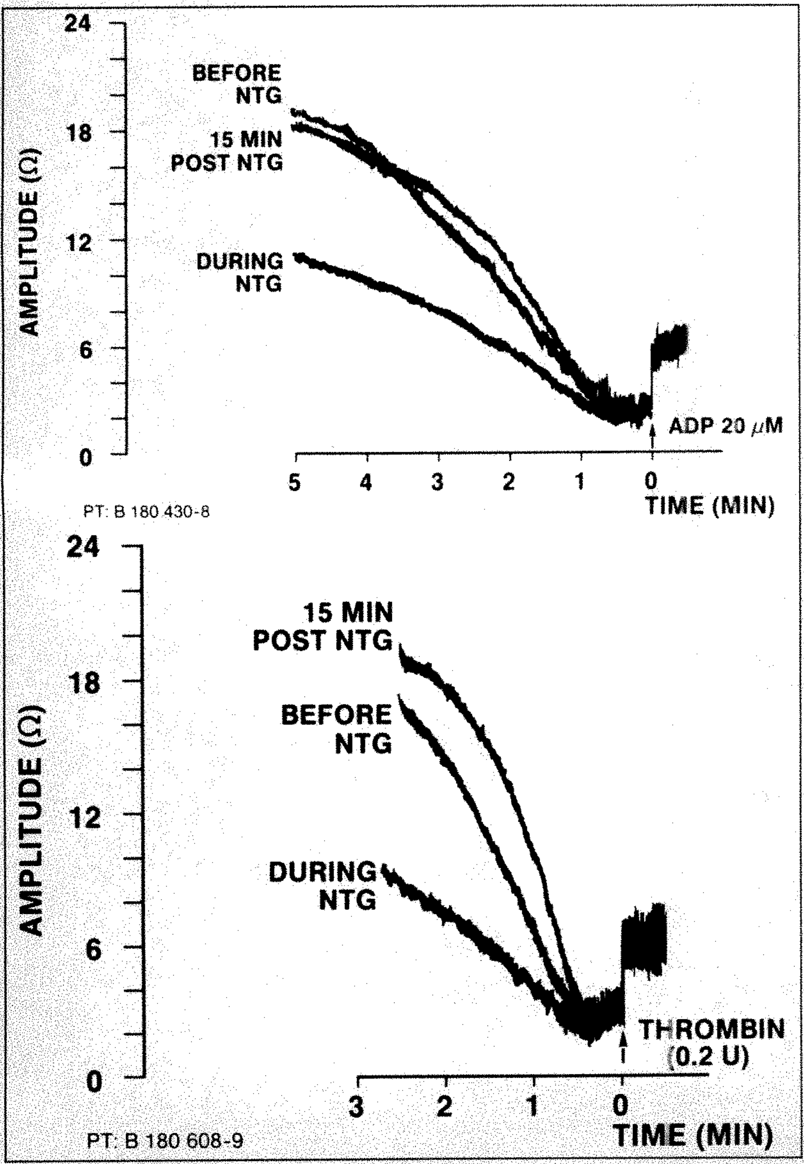

FIGURE 1. Typical examples of aggregation responses to adenosine diphosphate (ADP, *top*) and to thrombin (*bottom*) before, during, and after infusion of nitroglycerin (NTG). The amplitude of the curve is calibrated in ohms (Ω). Nitroglycerin inhibits platelet aggregation to both reagents and the effect is rapidly reversible after discontinuation of the drug.

physiologic saline using a dual channel impedance aggregometer (Chronolog Corp.).[18] The tests were initiated by adding 50 μl thrombin or ADP to final concentrations of 0.15 National Institutes of Health unit/ml or 20 μM, respectively. Materials and reagents in contact with blood, including the syringes for blood sampling and the aggregating agents, were kept strictly at 37°. This equipment was mobile and all studies were performed at the bedside. For each analysis, 4.5 ml of blood were drawn into preheated syringes containing 0.5 ml sodium citrate 3.8% with a pH of 7.4. Part of this blood was used for immediate testing within the first minute after sampling. The remaining blood was preserved at 22°C for 25 minutes before reincubation at 37°C for 5 minutes and testing.

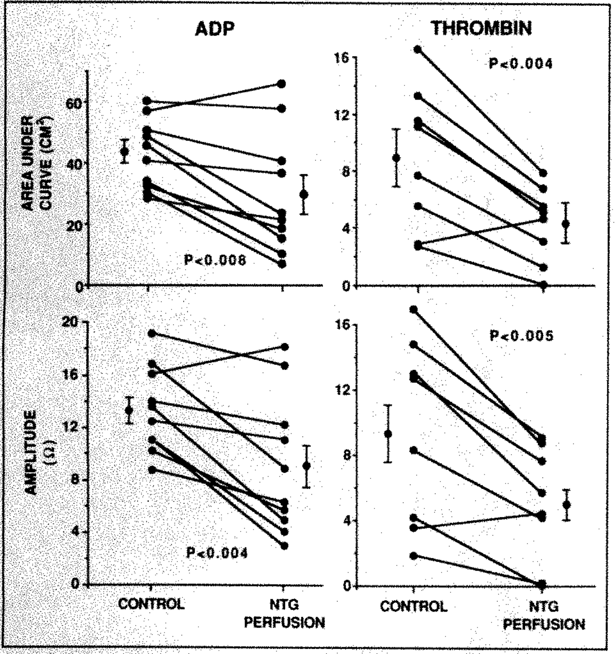

FIGURE 2. Individual responses to adenosine diphosphate (ADP, *left panels*) and to thrombin (*right panels*) before and during nitroglycerin (NTG) infusion. Two patients did not react to thrombin in the basal state and are not included. The area under the curve is shown in the *top panels* and the amplitude in ohms in the *lower panels*.

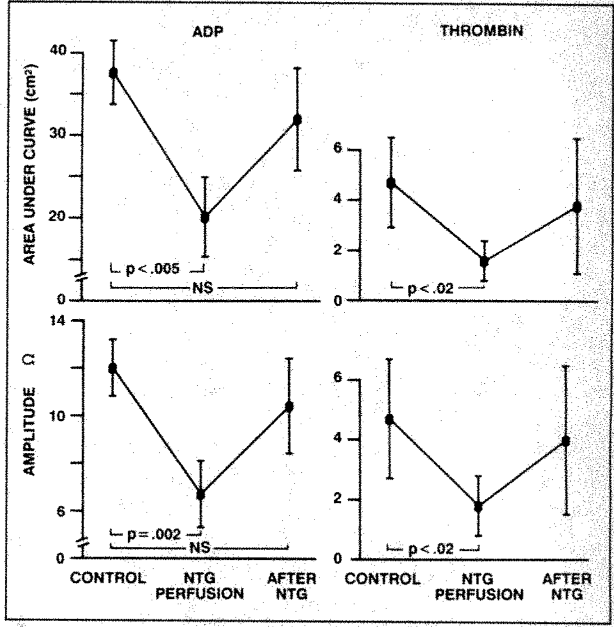

FIGURE 3. Mean results observed in the 6 patients who had platelet aggregation studies before, during and 15 minutes after discontinuation of the infusion of nitroglycerin (NTG). Surface areas (*top panels*) and amplitudes (*bottom panels*) of the aggregation curves show a return to baseline, preNTG values, 15 minutes after discontinuation of the infusion.

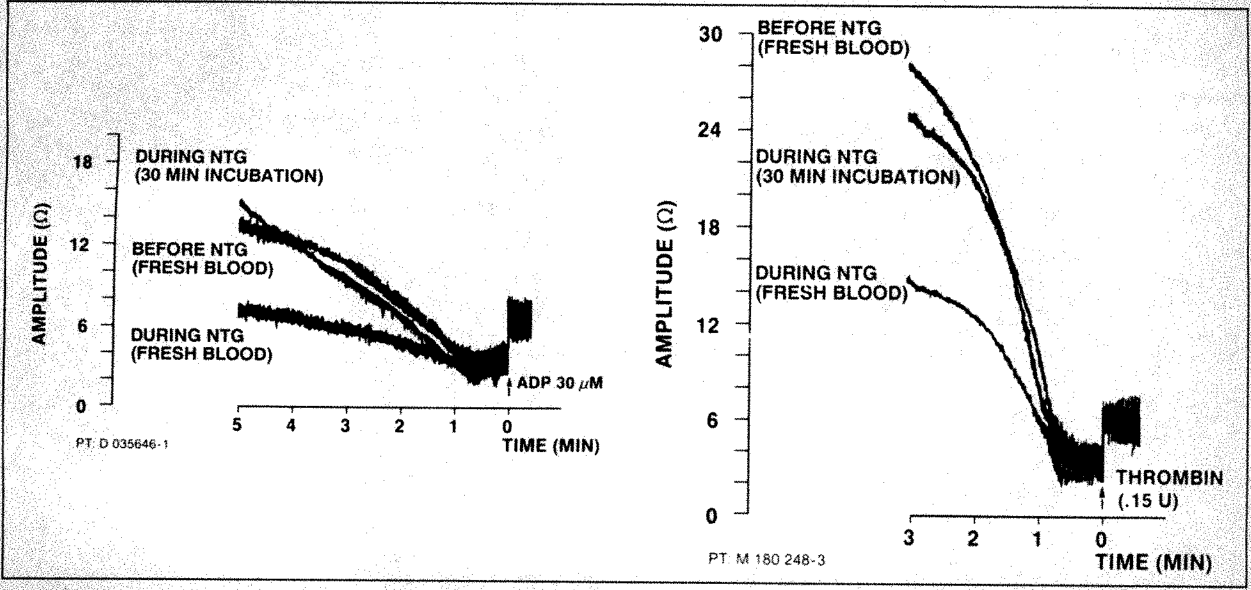

FIGURE 4. Typical examples of aggregation curves obtained before and during nitroglycerin (NTG) in blood tested immediately after withdrawal (fresh blood) and in same blood tested 30 minutes after incubation at room temperature. Response to adenosine diphosphate (ADP) is shown on the *left panel* and to thrombin in the *right panel*. The inhibitory effect of NTG is not detected in blood preserved at room temperature.

Platelet aggregation was quantified in terms of maximum amplitude (ohms) and surface area (cm^2) under the response-curve obtained 2 (thrombin) and 5 minutes (ADP) after addition of the aggregants.

Reproducibility of the method using fresh blood was validated on 2 blood samples collected 45 minutes apart in 14 patients without nitroglycerin in the intravenous perfusion of dextrose 5% in water. Results obtained on the second sample drawn after 45 minutes were respectively in percent: 111 ± 6 (amplitude), 108 ± 6 (surface area) with ADP, and 101 ± 5 (amplitude), 104 ± 5 (surface area) with thrombin, as compared to baseline values set at 100%. Differences were not statistically significant.

Statistical analyses: Results obtained before and during the perfusion of nitroglycerin were compared using the *t* test for paired comparisons. A p value <0.05 was considered significant.

RESULTS

Hemodynamic changes: The mean dose of nitroglycerin used was 1.19 μg/kg/min (range 0.4 to 1.9). The changes observed in heart rate and mean blood pressure for the individual patients are listed in Table I. All patients had a ≥10% decrease in mean arterial blood pressure except for 3 in whom incremental dosing was stopped because of headache. Heart rate increased by a mean of 6 beats/min from an average of 69 ± 3 ($p < 0.02$).

Platelet aggregation studies: A typical example of the response to nitroglycerin is shown in Figure 1. Testing aggregation to ADP and to thrombin in fresh blood revealed a 50% decrease during the perfusion of nitroglycerin and a return to prenitroglycerin control values 15 minutes after its discontinuation.

Figure 2 shows the response for all patients. In the basal state, samples from 2 patients failed to respond to thrombin and are not included. Nitroglycerin decreased the aggregation response to ADP or thrombin in all but 1 patient. In two-thirds, the decrease was >50% when the results of 1 test were considered and when the results with either test were considered, it was >50% in all patients. Overall estimation of aggregation indicates a decrease during nitroglycerin perfusion in the magnitude (amplitude of the curve) and extent of aggregation (surface area under the curve) by 44 and 47% with ADP and 62 and 66% with thrombin, respectively.

Inhibition of platelet aggregation by nitroglycerin was rapidly reversible, as indicated by a return to near control values 15 minutes after the discontinuation of the perfusion (Figures 1 and 3). The platelet response was not related to the magnitude of changes in blood pressure and in heart rate.

In contrast to the above results obtained on fresh blood, platelet aggregation remained unchanged during nitroglycerin administration when tested on preserved blood samples. A typical example is shown in Figure 4 where the inhibition of aggregation to thrombin by nitroglycerin is detected in fresh blood but no effect is detected in the deferred analysis. Figure 5 shows the results for the whole group of patients: platelet aggregation to ADP and to thrombin is similar in fresh and preserved blood before nitroglycerin. During nitroglycerin, the aggregation decreases significantly in fresh blood but is unchanged in preserved blood.

DISCUSSION

This study shows that nitroglycerin used at therapeutic doses can inhibit platelet function in patients with acute ischemic syndromes. The inhibitory effect is rapidly reversible after discontinuation of the drug. This observation extends to the clinical setting of previous experimental results showing a potent platelet inhibitory effect of nitroglycerin in vivo[15] and in vitro.[14] However, these results were observed only at concentrations of nitroglycerin >1 μg/ml, well above the therapeutic range.[9,16,17]

Other studies with platelet-rich plasma have failed to consistently show a platelet effect of intravenous and sublingual nitroglycerin,[9,10,12] although a prolongation in bleeding time suggested that such an effect could be present.[10] Fitzgerald et al[11] described an inhibition of epinephrine and arachidonic acid-induced aggregation in 1 of 5 patients investigated. De Caterina et al[13] studied the effect of a perfusion of isosorbide dinitrate in 11 patients with angina and reported a significant decrease in ADP and adrenalin-induced aggregation.[13] Paradoxically, the inhibition was present only at low doses and

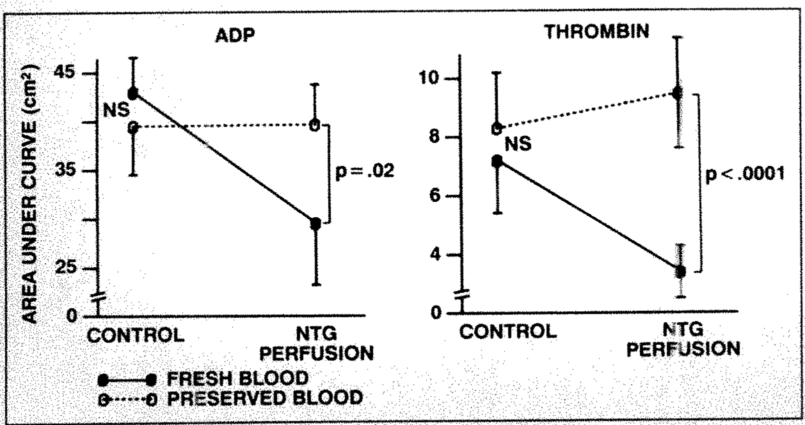

FIGURE 5. Mean results in 10 patients tested before and during nitroglycerin (NTG) in same blood sample tested immediately after withdrawal (fresh blood) and after 30 minutes at room temperature (preserved blood). Responses to adenosine diphosphate (ADP, *left panel*) and to thrombin (*right panel*) are similar. The inhibiting effect of nitroglycerin present in native blood is not detected in preserved blood.

the maximum effect was observed 60 minutes after discontinuation of the drug.

In this study, all patients showed an inhibition of >50% when the results of one or the other aggregating agents were considered; nitroglycerin inhibited aggregation to thrombin in all but 1 patient and aggregation to ADP in 8 of the 10 patients; the magnitude of the inhibition was of similar range among patients.

Mechanism of the inhibition: The exact mechanism of the inhibiting effect of nitroglycerin remains speculative. Although studies have suggested some interaction between nitroglycerin and prostacyclin synthesis and thromboxane A_2 inhibition,[19] others have failed to show such a relation.[12,16] Current evidences suggest that the nitrates may act by stimulating the guanylate cyclase enzyme leading to cyclic guanosine monophosphate production, which may be responsible for the vascular[20,21] and platelet effect[22] of nitroglycerin.

Study limitations: The impedance aggregometer has not been fully validated and additional studies are required to characterize its potential advantages and disadvantages. Discrepancies between this method and others may reflect adherence of other blood cells to the electrode.[23,24] However, under basal conditions, a good correlation is seen between the results obtained with the impedance aggregometer and the standard light transmission aggregometer,[18] with a higher sensitivity for the former to detect the effects of some aggregating and antiplatelet agents.[23,24] Indeed, in contrast to the optical test that uses platelet-rich plasma, the impedance aggregometer allows studies in the presence of all blood elements. Such analysis should theoretically be more representative of in vivo platelet behavior by avoiding platelet manipulation, centrifugation and loss of platelet-active blood factors. In addition, early and rapid analysis of blood may be critically important for detecting the effects of labile blood factors and drugs with short half-lives like nitroglycerin.

The study does not allow an insight into the mechanism of action of nitroglycerin. Whether the observed results represent a direct influence on platelet function or a nonspecific effect remains to be investigated by other techniques, such as measurement of platelet cyclic guanine monophosphate. The nitroglycerin-induced increase in autonomic tone could influence the distribution of platelets and their behavior. However, in this study, no correlation was observed between the inhibitory effect and the hemodynamic responses. The in vivo correlates of the observed effects on platelet function are not known and would require in vivo tests of platelet function. Indeed, a decrease in ex vivo platelet aggregation could reflect in vivo activation.[25] Finally, the study population consisted of patients with acute ischemic syndromes in whom platelets and blood factors are activated in relation to plaque rupture and fissure. Whether the observed inhibitory effect of nitroglycerin is dependent on this activation process or not will also need further investigation. A change in the clinical status of the patients is an unlikely explanation for the improvement noted with nitroglycerin because a return to the prenitroglycerin values was observed after discontinuation of the drug. Other drugs used in half the patients (calcium antagonists, captopril) also unlikely influenced the results since they were in a steady state administration.

Clinical relevance: The observation of decreased platelet aggregation with nitroglycerin raises a plausible hypothesis to explain many of the beneficial effects observed when the drug is used in unstable angina and myocardial infarction. Administration of nitroglycerin in acute myocardial infarction decreases the need for analgesics,[26] promotes patency of the infarct-related artery during fibrinolysis[7] and decreases infarct size.[6] A continuous infusion in unstable angina controls episodes of chest pain without significant changes in mean arterial pressure and heart rate and without the apparent development of tolerance to the drug.[27]

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Significance of Dipyridamole-Induced Transient Dilation of the Left Ventricle During Thallium-201 Scintigraphy in Suspected Coronary Artery Disease

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The occurrence and significance of transient dilation of the left ventricle during dipyridamole stress-redistribution thallium-201 scintigraphy was studied in 73 patients who underwent both dipyridamole thallium-201 study and coronary angiography. Transient dilation ratio was calculated from planar anterior images by dividing the computer-derived left ventricular area on the initial image by that of the 4-hour image. In 11 patients with normal coronary arteriograms or <50% coronary stenosis, the transient dilation ratio was 0.98 ± 0.046. An abnormal transient dilation ratio was defined as ≥1.12, representing ≥3 standard deviations above the mean normal value. When the 15 patients with an abnormal ratio were compared with the 58 with a normal ratio, the former group had a significantly higher frequency of 3 critical (≥90%) coronary stenoses (33 vs 5%), higher prevalence of collaterals (67 vs 24%), more extensive myocardial reversible defects by planar (71 vs 10%) or by single-photon emission computed tomography (87.5 vs 35%) imaging and a higher incidence of dipyridamole-induced anginal chest pain (53 vs 22%). No significant difference between the 2 groups was noted with respect to age, gender, prior myocardial infarction, single or double critical coronary stenosis, dipyridamole-induced ischemic electrocardiographic response and increased lung uptake. An abnormal transient dilation ratio of ≥1.12 was a specific marker of multivessel (87%) or 3-vessel (85%) critical coronary artery disease. Left ventricular transient dilation observed during dipyridamole thallium-201 scintigraphy is a marker of extensive myocardial ischemia caused by underlying extensive critical coronary stenosis and thus may be termed "transient ischemic dilation."

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Transient dilation of the left ventricle after exercise has been reported to be a marker of severe and extensive coronary artery disease in patients undergoing exercise-redistribution thallium-201 scintigraphy.[1,2] In patients who are unable to exercise adequately, dipyridamole infusion has been used as an alternative form of stress.[3-9] Although the accuracy of dipyridamole and exercise thallium-201 stress testing has been reported to be similar for detection of coronary artery disease,[5] these 2 modes of stress are quite different with respect to their effect on left ventricular preload, left ventricular afterload, myocardial oxygen demand and frequency of true ischemia.[3] Because of these underlying physiologic differences, the significance of transient dilation of the left ventricle observed after dipyridamole infusion may not be similar to that observed after exercise. We undertook this study to evaluate the frequency and determinants of dipyridamole-induced transient dilation of the left ventricle during thallium-201 scintigraphy.

METHODS

Patients: The study group consisted of 73 patients among those referred to our nuclear cardiology laboratory who had undergone dipyridamole stress-redistribution thallium-201 scintigraphy and coronary angiography within 5 months of one another without an intervening ischemic event. Patients who had previously undergone coronary artery bypass surgery or prior coronary angioplasty were excluded as were patients requiring aminophylline to reverse the effect of dipyridamole before completion of the anterior planar view. There were 34 men and 39 women aged 29 to 85 years (mean 68). Twenty-four patients had history of a prior documented myocardial infarction.

Dipyridamole thallium-201 imaging protocol: Dipyridamole, 0.56 mg/kg body weight, was infused intravenously over a 4-minute period with the patient in the supine position. Four minutes after discontinuation of infusion, the patients received 2 to 3.5 mCi of thallium-

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201 intravenously. Twelve-lead electrocardiograms, heart rate and blood pressure were obtained at the control stage before dipyridamole infusion and every minute thereafter for ≥12 minutes. Myocardial imaging started 10 minutes after thallium-201 injection. Forty-eight patients underwent planar imaging to obtain anterior, 45° and 85° left anterior oblique views (10 minutes per view). In 25 patients a 5-minute anterior view planar image was obtained followed by single-photon emission computerized tomography (SPECT). For SPECT, 32 projections were obtained over a 180° arc (from the 45° right anterior oblique to the 45° left posterior oblique views), each for 40 seconds. The redistribution images were obtained 3 to 5 hours after thallium-201 injection according to the same acquisition protocol that was used for the early postdipyridamole infusion study. With this protocol, planar images for all patients were obtained in the anterior view at 10 minutes and 3 to 5 hours after thallium-201 injection. For both planar and SPECT studies, images were acquired using a standard large field-of-view Anger camera equipped with 37 photomultiplier tubes, a one-quarter-inch-thick sodium iodide crystal and a parallel-hole collimator. A 20 and a 10% energy window was centered on the 69 to 83 KeV and the 167 KeV photopeaks of thallium-201, respectively. For planar imaging, a high resolution collimator was used and images were stored on 128 × 128, 8 bit matrix. For the SPECT study, an all-purpose collimator was used and images were stored on 64 × 64, 8- bit matrix.

Quantitation of transient dilation of the left ventricle: The anterior view planar images were used for quantitation of transient dilation of the left ventricle in all patients. After interpolative background subtraction and 9-point smoothing, the epicardial border of the left ventricle was manually assigned by an experienced operator on both stress and redistribution images using an electronic marker (Figure 1). In patients with severe perfusion defects in whom the epicardial border could not be clearly defined, the computer operator assigned the region that most closely approximated the typical left ventricular shape. The left ventricular area encompassed by the region of interest was then determined by the computer and was expressed as number of pixels contained within the epicardial border. Transient dilation ratio was then calculated by dividing the left ventricular area on the stress image (expressed as number of pixels) by the left ventricular area on the 4-hour redistribution image.

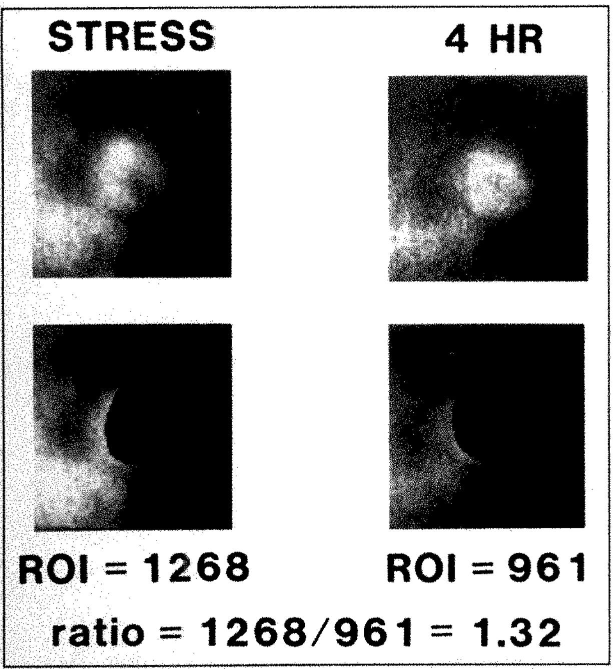

FIGURE 1. Method for quantitating transient dilation ratio in a patient with 3-vessel severe coronary disease. *Top,* stress *(left)* and redistribution *(right)* planar anterior images are shown. *Bottom,* left ventricular regions of interest (ROI) manually assigned and the transient dilation ratio value calculated by dividing stress by 4-hour regions-of-interest values.

Visual interpretation of thallium-201 scintigrams: Thallium-201 images were interpreted for myocardial perfusion and degree of lung uptake by the consensus of 2 experienced observers who did not have knowledge of the other test results. For interpretation of myocardial perfusion on planar images, the left ventricle was divided into 5 segments in each view and segmental thallium-201 uptake was evaluated using a 4-point scoring system where 0 = normal uptake, 1 = slightly reduced uptake, 2 = moderately reduced uptake, and 3 = severely reduced uptake. For tomographic image analysis, the short axis and the apical portion of the vertical long axis were assessed according to a previously described method.[10] The thallium-201 myocardial tomograms were divided into 20 segments assigned on 6 evenly spaced regions in the apical, midventricular and basal cuts of the short-axis views and the anteroapical and inferoapical segments of the midvertical long-axis cut. Thallium-201 uptake was scored according to the same 4-point scoring system that was used for planar image analysis. Lung uptake of thallium-201 was scored visually as 0 = no lung uptake, 1 = mild lung uptake, 2 = moderate uptake with intensity of uptake less myocardium uptake, and 3 = severe lung uptake with an intensity similar to that of the myocardium.[11]

For both myocardial and lung uptake analysis, a score of ≥2 was considered definitely abnormal. The severity of perfusion abnormality was calculated by summing scores of all myocardial segments. Reversibility score was defined as the difference between the stress and redistribution defect severity scores. Defect reversibility was considered to be extensive if the reversibility score was >7. To assess clarity and definition of endocardial border on the anterior view and the presence and significance of transient endocardial dilation of the left ventricle, 43 of 73 studies were randomly selected. The definition of endocardial and epicardial borders was visually scored as poor, average or good. Transient endocardial dilation was defined as a larger left ventricular cavity on the stress anterior image than on the 4-hour redistribution image.

Definition of ischemic clinical and electrocardiographic responses to dipyridamole: The clinical response was considered ischemic during dipyridamole infusion or during the recovery period if the patient's angina was reproduced or if chest pain had characteristics of typical angina. The electrocardiographic response was considered ischemic if ≥1 mm of horizontal or downsloping ST depression or ≥1.5 mm of upsloping ST depression was noted at 0.08 second after the J point. Dipyridamole-induced electrocardiographic changes in 8 patients in whom the baseline electrocardiogram showed left bundle branch block (5 patients) or left ventricular hypertrophy (3 patients) were deemed nondiagnostic.

Coronary angiography: All patients underwent cardiac catheterization and selective coronary arteriography using the Judkins technique. Coronary arteriography was performed in 28 patients before and in 45 patients after thallium-201 testing. The mean interval between thallium-201 testing and angiography was 34 days (median 6, range 1 to 150). Coronary arteriograms were visually analyzed by the consensus of 2 experienced observers who were unaware of the thallium-201 test results. The most severe narrowing of the lumen in any projection was determined as <50%, ≥50% to <90% and ≥90%. With respect to extent and severity of coronary artery disease, 11 patients had a normal coronary arteriogram or a maximal luminal diameter coronary artery narrowing of <50%. Sixteen patients had coronary artery stenoses of ≥50% to <90% involving 1 or multiple coronary arteries. In the remaining 46 patients who had coronary stenosis of ≥90% (critical stenosis), stenosis involved 1 vessel in 25, 2 vessels in 13 and 3 vessels in 8 patients. Among these 8 patients, there was 1 patient who also had 80% left main disease. Collaterals (visible retrograde opacification of occluded or severely stenosed coronary arteries) were observed in 24 of 73 patients.

Statistical analysis: To determine the univariate significance of different variables with respect to normal or abnormal transient dilation ratios, a Fisher's exact test for the noncontinuous variables and a 2 sample *t* test for the continuous variables were used. To determine the relative significance of the univariate parameters, a stepwise logistic regression was done using all variables that were significant with the univariate analysis.

To evaluate the importance of different variables for predicting the presence of multiple (≥2) vessels with critical stenosis as well as for predicting the presence of 3-vessel critical stenosis, the univariate significance of the variables was first determined. To determine the relative significance of the univariate parameters for predicting multiple-vessel critical stenosis, a stepwise logistic regression was done using all variables that were significant with the univariate analysis. To determine the improvement in predicting triple critical coronary stenosis with the presence of abnormal transient dilation ratio, 2 logistic regression models were compared; in the first set all variables of interest except transient dilation ratio variable were considered and in the second set all variables were included. To compare between planar and SPECT reversibility scores, a 2-sample *t* test was used. For all analyses, significance tests were done at p = 0.05.

RESULTS

Transient dilation ratio in patients with normal coronary arteriograms: The mean transient dilation ratio in the 11 patients who had normal coronary arteriograms was 0.98 ± 0.0406. The abnormal transient dilation ratio was defined as mean + 3 standard deviations

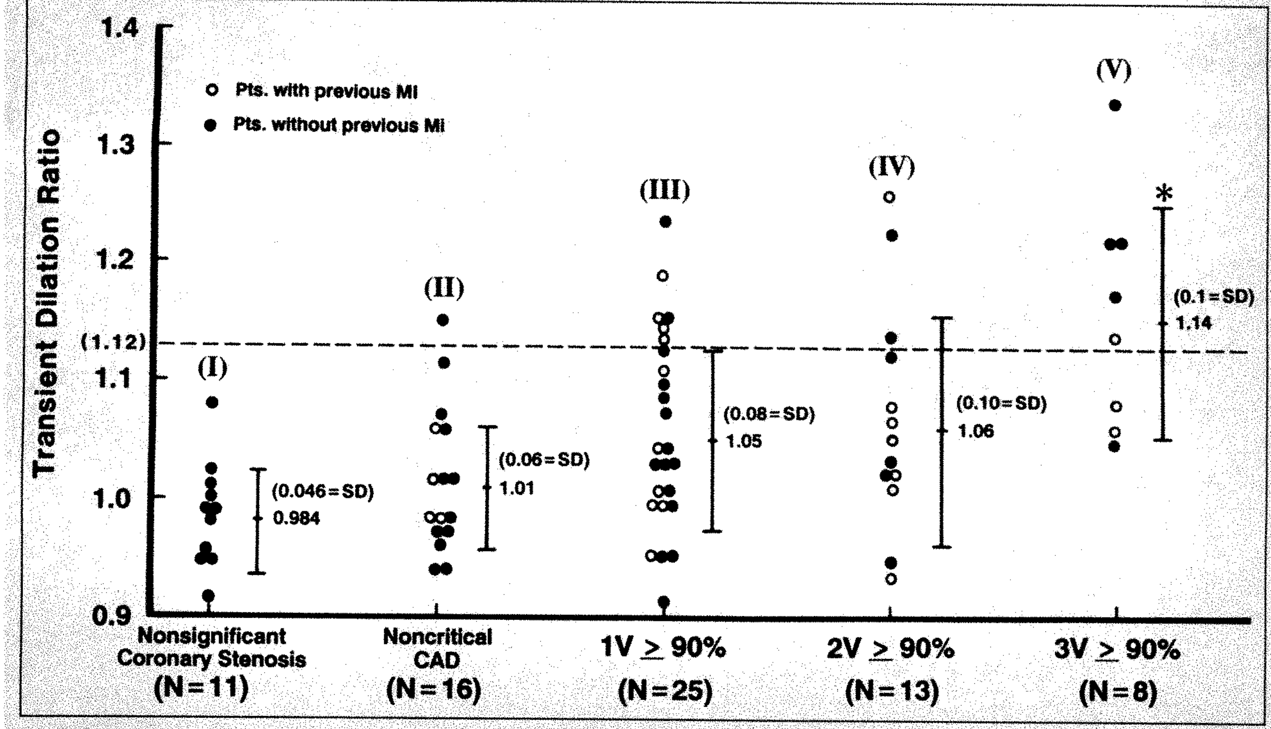

FIGURE 2. Relation between transient dilation ratio and presence, extent and severity of coronary artery disease (CAD) in patients with and without prior myocardial infarction (MI). SD = standard deviation; V = vessel; *p <0.05 vs groups I, II, III and IV.

TABLE I Prevalence of Angiographic, Scintigraphic and Clinical Variables in Patients With and Without Transient Dilation of the Left Ventricle in Dipyridamole Testing

	Transient Dilation		
	<1.12 (n = 58)	≥1.12 (n = 15)	p Value
Age (years)	68 ± 1	67 ± 3	NS
Gender (% men)	47%	47%	NS
Prior myocardial infarction	33%	33%	NS
Ischemic ECG response*	10% (5/50)	20% (3/15)	NS
Ischemic clinical response	22%	53%	0.05
No. of coronary arteries narrowed ≥90% in diameter			
1	33%	40%	NS
2	17%	20%	NS
3	5%	33%	0.001
Presence of collaterals	24%	67%	<0.01
Abnormal lung uptake	12%	7%	NS
Reversibility score >7			
Planar (n = 48)	10% (4/41)	71% (5/7)	<0.001
SPECT (n = 25)	35% (6/17)	87.5% (7/8)	<0.01

* The 8 patients with left bundle branch block or with left ventricular hypertrophy on their baseline electrocardiograms were excluded for this analysis.
ECG = electrocardiographic; NS = not significant; SPECT = single-photon emission computed tomography.

(0.98 + 0.14 = 1.12). Based on this definition, 47 of 62 patients with coronary disease and 11 of 11 patients with normal coronary arteries had a normal transient dilation ratio (Figure 2).

Results of univariate analysis for predictors of abnormal transient dilation ratio: Table I lists the results of univariant analysis for the significance of multiple variables that were compared between the 15 patients with and the 58 patients without an abnormal transient dilation ratio. No significant difference between the 2 groups was noted with respect to age, gender, prevalence of previous myocardial infarction, dipyridamole-induced increased lung uptake of thallium-201, ischemic electrocardiographic response, or the prevalence of 1- or 2-vessel critical stenoses. The significant univariant parameters were the prevalence of 3-vessel critical stenoses (33 vs 5%), prevalence of collaterals (67 vs 24%), extensive reversibility by planar imaging (71 vs 10%) or by SPECT imaging (87.5 vs 35%), and dipyridamole-induced angina (53 vs 22%).

Transient dilation ratio was found to be highly correlated with the reversibility score assessed whether by planar imaging or SPECT. The correlation coefficients between transient dilation ratio and reversibility score obtained from SPECT and planar images were 0.66 ($p < 0.001$) and 0.50 ($p < 0.001$), respectively. Table II compares reversibility scores by either planar or SPECT technique between patients with and without an abnormal transient dilation ratio. The reversibility score was significantly higher in patients with abnormal transient dilation ratio regardless of the imaging technique used. Furthermore, among a total of 15 patients with abnormal transient dilation ratio, there was no statistical difference between the reversibility scores in the 7 patients who underwent planar imaging vs the 8 patients who had SPECT imaging.

TABLE II Comparison of Reversibility Score Evaluated by Planar and SPECT Imaging in Patients With and Without Abnormal Transient Dilation Ratio

	Transient Dilation	
	<1.12 (n = 58)	≥1.12 (n = 15)
Reversibility score Planar (n = 48)	2.6 ± 0.5 (n = 41)	9.4 ± 1.9* (n = 7)
Reversibility score SPECT (n = 25)	4.4 ± 0.9 (n = 17)	13.1 ± 2.1* (n = 8)

* $p < 0.01$ versus patients with transient dilation ratio <1.12.
SPECT = single-photon emission computed tomography.

Multivariate analysis for prediction of abnormal transient dilation ratio: The multivariate analysis showed that the reversibility score, followed by number of coronary arteries with critical stenosis and ischemic clinical response to dipyridamole infusion, was the most significant predictor of an abnormal transient dilation ratio.

Multivariate analysis for prediction of multivessel critical coronary stenosis: The transient dilation ratio had significant predictive value ($p < 0.05$) for the presence of multivessel critical stenosis. Marginally significant predictive value ($0.05 < p < 0.10$) for prediction of patients with multivessel critical disease was found for the variables of ischemic electrocardiographic response, reversibility score and age.

Improvement in prediction of 3-vessel critical coronary disease by presence of abnormal transient dilation ratio: When the stepwise logistic regression was run using all variables of interest except the transient dilation variable, an ischemic electrocardiographic response to dipyridamole was found to be the only significant variable. When all variables were entered into the logistic regression concurrently, the transient dilation ratio significantly improved the prediction ($p < 0.05$). Age also significantly improved the prediction ($p < 0.05$). No other variable contributed to the prediction. Logistic re-

TABLE III Sensitivity and Specificity of Transient Dilation Ratio for Identification of Patients with Three- and Multiple-Vessel Critical Coronary Artery Stenoses

	Three-Vessel Critical Coronary Artery Stenoses		Multiple Vessel Critical Coronary Artery Stenoses	
	Sensitivity	Specificity	Sensitivity	Specificity
Patients without prior myocardial infarction	80% (4/5)	89% (39/44)	55% (6/11)	92% (35/38)
Patients with prior myocardial infarction	33% (1/3)	76% (16/21)	20% (2/10)	71% (10/14)
All patients	62.5% (5/8)	85% (55/65)	38% (8/21)	87% (45/52)

gression analysis showed that the transient dilation ratio threshold of 1.12 corresponded to the highest percent total number of patients with triple critical coronary disease (83%) who were correctly identified.

Sensitivity and specificity of transient dilation ratio for identification of patients with multiple and those with 3-vessel critical stenoses: Table III summarizes the results. Overall, transient dilation ratio was specific for identification of these patients but was not sensitive except in the small subgroups of patients without prior myocardial infarction who had 3-vessel critical stenoses.

Transient endocardial dilation of the left ventricle: Twenty-two of the 43 studies (51%) randomly selected to assess endocardial border demonstrated a poorly defined endocardial border, whereas all studies had well-defined epicardial borders. Six of these 43 studies demonstrated transient endocardial dilation without epicardial dilation. All 6 patients had multivessel coronary disease which was critical in 4.

DISCUSSION

It has been previously observed that transient dilation of the left ventricle during recovery from exercise occurs in 26% of patients undergoing exercise thallium-201 testing and has been associated with a high prevalence of multivessel critical coronary stenoses; this finding suggests that exercise-induced transient dilation is a sign of severe and extensive ischemia.[2] This study of the frequency and determinants of transient dilation of the left ventricle in patients undergoing dipyridamole stress-redistribution thallium-201 studies demonstrated that an abnormal transient dilation ratio occurred in 20.5% (15 of 73) of the included patients. This prevalence appears to be slightly lower than that observed with the exercise redistribution thallium-201 study. Because relatively sicker patients are referred for subsequent coronary angiography, the stated prevalence of left ventricular transient dilation in these studies may be overestimated. This study as well as a previous study[2] uses measurements of the epicardial border of the left ventricle on the anterior view. Other investigators have suggested that transient endocardial dilation of the left ventricle may be more sensitive for detecting severe and extensive ischemia. In 22 of 43 (51%) randomly selected studies, the definition of the endocardial border was problematic to the extent that the left ventricular cavity could not be seen to allow assessment of transient dilation.

The mean transient dilation ratio with dipyridamole testing in patients with normal or <50% luminal coronary artery narrowing was 0.98, which showed a trend toward a slightly lower value than that previously reported in patients undergoing exercise testing (1.02).[2] This trend may be due to a different status of ventricular afterload and preload in the early phase of recovery from these 2 different modes of stress. The prevalence of increased lung thallium uptake was not greater in the 15 patients with transient dilation of the left ventricle. A quantitated lung/myocardial ratio might have shown an abnormal ratio in this subgroup of patients.

The high prevalence of collateral blood flow to vessels with severe coronary lesions found in this study is of particular interest. It has been well demonstrated that dipyridamole is a potent coronary vasodilator, increasing myocardial blood flow 3 to 5 times above the resting level in myocardial regions subtended by normal coronary arteries.[3,4] Since the hyperemic response is attenuated in areas of myocardium subtended by diseased coronary arteries, inhomogeneity of coronary blood flow is created, causing thallium-201 myocardial perfusion defects. In vessels with critical lesions, maximal arterial vasodilation may already be present at rest. With reduction in perfusion pressure as a result of a modest decrease in systolic and diastolic blood pressure associated with dipyridamole infusion, a true "coronary steal" may be induced resulting in myocardial ischemia.[12-16] This effect would be expected to be accentuated in regions that are dependent on collateral flow at baseline. Our results suggest that dipyridamole-induced transient dilation is more prevalent in the subgroup with collaterals, probably because of more extensive and severe true ischemia. This is consistent with the findings of Becker.[12]

We found that the transient dilation phenomenon provides information about extensive critical coronary disease that is additive to other routinely analyzed clinical, electrocardiographic, and myocardial and pulmonary thallium-201 parameters.

These findings underscore the importance of our proposed protocol for SPECT imaging which includes acquisition of a 5-minute anterior view before the procedure. In the absence of this initial 5-minute anterior view, it is likely that transient ischemic dilation of the left ventricle could not be recognized on SPECT images in most patients who might have had this finding very early after dipyridamole. We have previously observed that not infrequently, transient dilation is only observed on the anterior image (15 minutes after injection of thallium-201) but not on the 45° and 85° left anterior oblique views at 25 and 35 minutes after injection of thallium-201. By the time of completion of tomographic imaging, which is ≥30 minutes after the injection of thallium-201, transient dilation would probably subside.

Dipyridamole-induced transient dilation of the left ventricle was a specific marker of 3-vessel critical coronary in both subgroups of patients with (76%) and without (89%) prior myocardial infarction. However, the abnormal transient dilation ratio was a sensitive indicator of 3-vessel critical stenoses only in patients without prior myocardial infarction (80 vs 33%), further confirming that this phenomenon is of ischemic origin.

Study limitations: Interobserver variability was not assessed in the study. However, our previous study experience with exercise-redistribution thallium-201 studies has shown acceptable interobserver variability.[2] The extent of reversibility of thallium-201 defects was analyzed by semiquantitative consensus visual inspection. An objective computerized method for assessment of the extent and severity of thallium-201 defects is in the final stages of validation in our institution. In this study, 25 patients underwent SPECT imaging and the remaining 48 planar imaging. Although it is possible that the imaging method will affect assessment of the total reversibility score, we found that the results were not significantly different in the 2 subgroups. We also found that regardless of the imaging method used, patients had a significantly higher reversibility scoring index with than without an abnormal transient dilation ratio.

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Coronary Sinus Lysophosphatidylcholine Accumulation During Rapid Atrial Pacing

Steven P. Sedlis, MD, Jeffrey M. Sequeira, MS, and Henry M. Altszuler, MD

The purpose of this study was to determine whether lysophosphatidylcholine (LPC) release from the myocardium could be detected in patients with pacing-induced ischemia. We measured LPC levels in plasma obtained from the coronary sinus in 20 patients undergoing diagnostic atrial pacing stress tests. In 14 patients with pacing-induced ischemia, coronary sinus LPC concentration rose from 69.1 ± 5.3 μM at baseline to 101.7 ± 9.0 μM at 4 minutes and to 178.0 ± 18.0 μM at peak pacing ($p < 0.01$). LPC did not increase significantly in 6 nonischemic patients (from 60.8 ± 7.8 μM at baseline to 70.2 ± 7.6 μM at peak pacing, difference not significant). LPC did not increase in mixed venous or arterial blood from ischemic patients. Thus, coronary sinus LPC accumulation may be an early marker of ischemia.

(Am J Cardiol 1990;66:695–698)

Lysophosphatidylcholine (LPC), an arrhythmogenic metabolite of membrane phosphatidylcholine, accumulates rapidly during cardiac ischemia in animals.[1-4] The importance of LPC in the pathogenesis of ischemic injury in man is unclear because myocardial concentrations of lysolipids vary markedly between species[5-7] and LPC accumulation has not been previously documented in ischemic human hearts. Thus, we sought to determine whether LPC accumulation occurs in the coronary sinus during atrial pacing in humans.

METHODS

Twenty male patients undergoing diagnostic coronary sinus pacing stress tests were enrolled in the study. Their mean age was 60.8 ± 2.3 years (range 40 to 80). Informed consent for this study was obtained from all patients. All patients also underwent right- and left-sided heart catheterization and coronary arteriography. Cardiac medications were discontinued 24 hours before stress testing. Pacing began at the sinus rate and was increased by 20 beats/min every 2 minutes until the rate reached 160 beats/min or until angina accompanied by ischemic changes on the electrocardiogram developed. Intravenous atropine was administered if atrioventricular conduction block developed before any study end points were observed. Stress tests were classified as positive if >1.0 mm ST-segment depressions were noted or if coronary sinus lactate consumption decreased at peak pacing rate.

One-milliliter samples of whole blood were collected from the coronary sinus at 2-minute intervals for a total of 30 minutes. Samples were drawn into dry syringes, immediately transferred to glass tubes containing citrate (100 μl) and centrifuged; 100 μl of the plasma was added to 3 ml chloroform:methanol (1:2) and centrifuged to remove denatured protein. The supernatant was extracted and phospholipids were separated by high-performance liquid chromatography.[8] Yield of added LPC (internal standard) was increased to 99% by repeated extractions (3) of the denatured protein pellet. Phospholipids were quantified by a modified Chen phosphate assay.[9] The assay could detect 2.0 nmol of LPC added to 100 μl of normal human plasma. LPC concentration in peripheral venous blood of 8 normal volunteers was 55.3 ± 8.6 μM. This was not significantly different from LPC concentration in peripheral venous, arterial or coronary sinus blood at rest or during atrial pacing at the sinus rate in patients undergoing atrial pacing stress tests.

Coronary sinus blood flow was measured at baseline, at peak pacing rate and 30 minutes after the onset of pacing in the last 13 patients by the thermodilution

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TABLE I Results of Positive and Negative Stress Tests in 20 Patients

Coronary Arteries with >50% Diameter Narrowing	Lactate Consumption (mmol · ml/min)		LPC Concentration (μM)		Net LPC Accumulation (μmol/min)
	Baseline	Peak Pacing	Baseline	Peak Pacing	
Positive stress tests					
LAD, RCA, LC	—	—	45.4	202.1	—
LAD	—	—	75.6	213.8	—
LAD, RCA, LC	—	—	74.9	273.4	—
LAD, RCA	—	—	38.8	108.4	—
LCxA	—	—	39.8	130.3	—
LAD, RCA, LC	—	—	57.3	81.2	—
LAD, RCA	—	—	86.9	205.7	21.3
LAD	—	—	93.2	129.3	4.7
LAD, RCA, LC	16.2	7	60.3	108.7	6.8
LAD	17	8.4	64.8	188.2	17.3
LAD, RCA, LC	12.4	7	70.6	262.8	46.9
RCA, LC	24	*10.7	92.5	287.3	19.5
LAD, RCA, LC	15.1	7.2	100.7	188.6	17.4
RCA	19.2	7.5	64.3	112.3	12.0
Negative stress tests					
LAD, LC	—	—	33.0	40.0	—
LC	23.3	26.6	53.7	87.1	3.2
0	4.8	9.6	49.9	60.2	0.8
0	45.9	49.1	86.6	90.1	0.7
0	6.9	15.2	75.1	76.3	0.1
0	13.3	30.8	66.3	67.5	0.2

* Data not obtained.
LAD = left anterior descending artery; LC = left circumflex artery; LPC = lysophosphatidylcholine; RCA = right coronary artery.

technique using the Baim coronary sinus catheter and analyzer system (Elecath, Inc.).[10] Lactate consumption [(arterial lactate-coronary sinus lactate) × coronary sinus blood flow] was measured in the last 11 patients.[11,12] In 4 patients, simultaneous great cardiac vein blood flow was also measured. All waveforms used for analysis showed the phasic pattern characteristic of coronary sinus and great cardiac vein blood flow.

Results are expressed as the mean ± the standard error. Student's *t* test for unpaired samples and the Mann-Whitney nonparametric U test were used to test differences between group means for single comparisons. Tukey's honestly significant difference was used when group means were compared at >2 time points. Differences from baseline within a group were tested using Student's *t* test for paired samples. Values for p are those for single-tail tests with a p value <0.05 indicating a statistically significant difference.

RESULTS

Coronary sinus LPC concentration increased in 14 patients with positive stress tests (Table I) from 69.1 ± 5.3 μM at baseline to 178.0 ± 18.0 μM at peak pacing ($p < 0.001$). In contrast, coronary sinus LPC concentration did not increase significantly in 6 patients with negative stress tests from 60.8 ± 7.8 μM at baseline to 70.2 ± 7.6 μM at peak pacing (difference not significant). The rate of coronary sinus LPC accumulation (increase in coronary sinus LPC concentration × coronary sinus blood flow) during peak pacing was 18.2 ± 4.6 μmol/min in 8 ischemic patients and only 0.9 ± 0.6 μmol/min in 5 patients with negative stress tests ($p < 0.01$). LPC increased only in the coronary sinus, not in mixed venous or arterial blood. Levels of phosphatidylcholine did not change significantly.

Coronary sinus LPC concentration in patients with positive stress tests increased significantly after only 4 minutes of pacing ([to 101.7 ± 9.0 μM $p < 0.01$] Figure 1). The rate of increase of coronary sinus LPC concentration between 4 and 10 minutes of pacing in patients with positive stress tests was linear and fit best by the function $y = 10.084x + 62.967$. Coronary sinus LPC concentration in patients with positive stress tests reached maximal levels at peak pacing rate and slowly declined after the cessation of pacing (Figure 2).

To better localize the source of LPC, rates of coronary sinus and great cardiac vein LPC accumulation at peak pacing (increase in LPC concentration × blood flow) were measured simultaneously in 4 patients. The great cardiac vein empties into the coronary sinus and predominantly drains myocardium supplied by the left anterior descending artery. In a patient with left anterior descending artery disease, 97% of total LPC accumulation at peak pacing was of great cardiac vein origin. In contrast, in 2 patients with circumflex and or right coronary artery disease, only 23 and 35%, respectively, of total LPC accumulation at peak pacing were of great cardiac vein origin. In a patient with 3-vessel disease, 45% of total LPC accumulation at peak pacing was of great cardiac vein origin.

DISCUSSION

Coronary sinus LPC accumulation appears to be a sensitive, specific and early marker of ischemia in humans. Coronary sinus LPC concentration increased significantly within 4 minutes of the onset of atrial pacing and preceded clinical indicators of ischemia. LPC increased only in patients with positive stress tests and only in venous effluents from the myocardium. The specificity of LPC accumulation for ischemia is further suggested by the results obtained by selective catheterization of the great cardiac vein. For example, in a patient with left anterior descending artery disease, LPC concentration was higher in the great cardiac vein than in the coronary sinus where it was diluted by nonischemic effluent. In contrast, in 2 patients with positive stress tests, but without significant disease of the left anterior descending artery, LPC accumulated in the coronary sinus, but only minimal quantities of LPC could be detected in the great cardiac vein. Further studies are needed to confirm that LPC release is a marker of regional ischemia.

The degree of LPC accumulation in the coronary sinus may reflect the severity of ischemia. For example, the 3 patients in our study with the highest net LPC accumulation all had severe ischemia manifested by either marked electrocardiogram or hemodynamic changes. No patients in our study had arrhythmias, so we cannot make any conclusion regarding the role of LPC in the pathogenesis of ischemic ventricular arrhythmias in patients. Further investigations with additional endpoints (such as change in ventricular function and degree of thallium redistribution with ischemia) are needed to determine whether the degree of coronary sinus LPC accumulation is a marker of the extent as well as the presence of ischemia.

Coronary sinus LPC accumulation during pacing-induced ischemia most likely results from inhibition of LPC metabolism. LPC, a product of phospholipase A_2-mediated hydrolysis of membrane phosphatidylcholine,[13] is itself rapidly metabolized.[14,15] Ischemia results in inhibition of these normal pathways of LPC metabolism in the myocardium in animal models[14,15] that permits lysolipid accumulation. Catecholamine-mediated activation of phospholipase A_2 may also predispose to LPC accumulation, but this is unlikely to have been the sole mechanism leading to LPC accumulation in our patients because coronary sinus phosphatidylcholine did not decrease. Furthermore, atrial pacing stress appears to augment sympathetic tone more in control subjects than in ischemic patients,[16] whereas in our study LPC increased in ischemic patients but not in control subjects. Plasma proteins bind LPC.[1] Because protein binding may represent a mechanism for washout of LPC from ischemic myocardial tissue, we cannot be certain of the concentration of free LPC in the ischemic zone in our patients.

The purpose of our study was not to determine whether LPC is a mediator of ischemic injury. There is considerable experimental evidence, however, to suggest

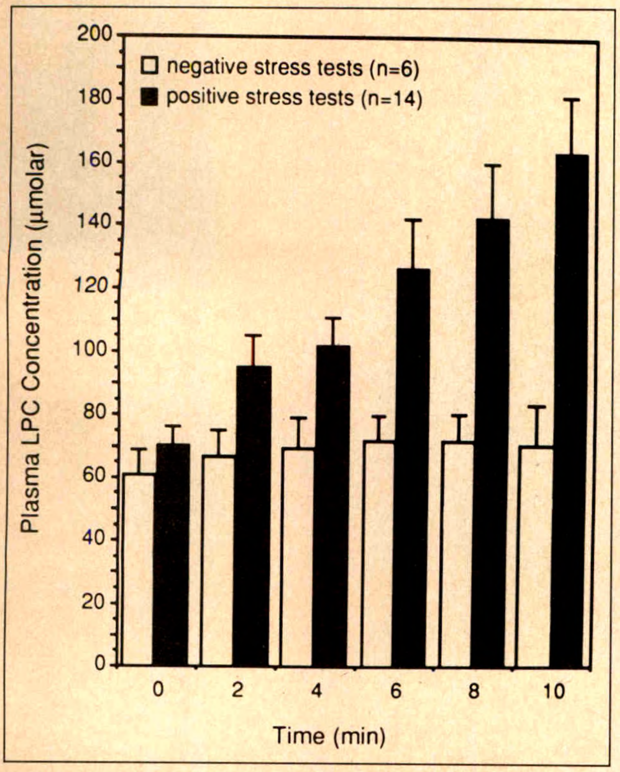

FIGURE 1. Coronary sinus lysophosphatidylcholine (LPC) concentration during atrial pacing. Mean values for coronary sinus LPC concentration versus time are plotted separately for 14 patients with positive stress tests and 6 patients with negative stress tests. In patients with positive stress tests, mean coronary sinus LPC concentration increased significantly within 4 minutes ($p < 0.01$).

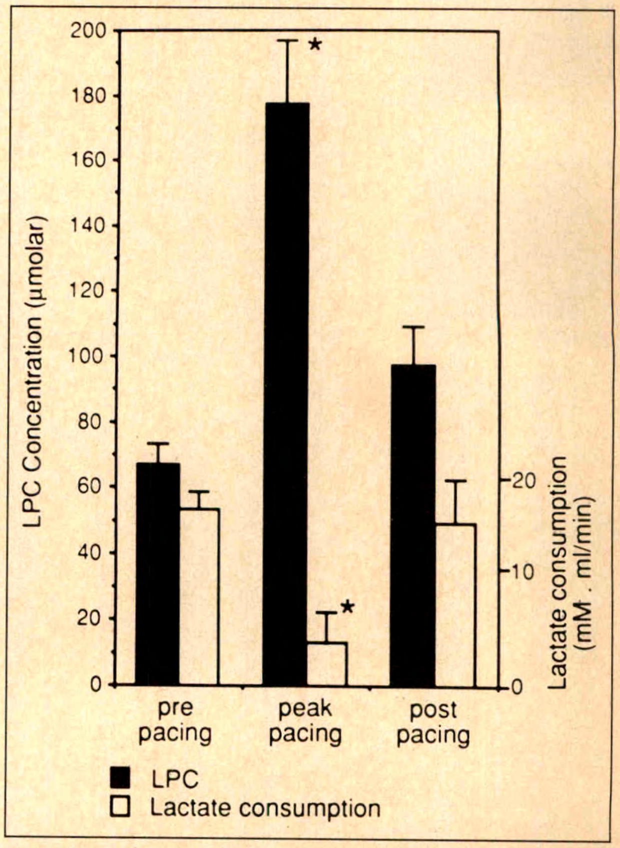

FIGURE 2. Coronary sinus lysophosphatidylcholine (LPC) concentration and lactate consumption in 14 patients with positive stress tests at baseline, at peak pacing and 30 minutes after onset of pacing. Coronary sinus LPC concentration was highest and lactate consumption was lowest at peak pacing. * $p < 0.01$ compared to pre- and postpacing.

that LPC plays a role in the pathogenesis of ischemic injury. For example, LPC is arrhythmogenic in vitro[1-4]; LPC can depress contractile function of cardiac myocytes,[17] and high concentrations of free LPC can irreversibly injure myocytes.[8,18] The mechanism of LPC-induced injury is not yet fully understood. LPC alters membrane fluidity and permeability leading to abnormalities in ion flux.[19] Production and washout of LPC may also lead to depletion of structural phospholipids from the myocardium.[20]

Thus, LPC, a possible mediator of myocardial injury, accumulates rapidly in the coronary sinus during cardiac ischemia induced by atrial pacing in patients with coronary artery disease. We hypothesize that coronary sinus LPC accumulation represents washout of LPC produced in ischemic myocardium. Thus, LPC may accumulate in the myocardium during cardiac ischemia in quantities sufficient to contribute to the pathogenesis of ischemic injury in man.

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Clinical and Pathophysiologic Correlates of ST-T-Wave Abnormalities in Coronary Artery Disease

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Clinical, hemodynamic and coronary angiographic data from 9,801 patients were evaluated to determine the correlates of ST-segment depression, with or without T-wave inversion, on the resting routine electrocardiogram. The relative risk (RR) of having a measured clinical or angiographic variable was computed whether or not ST-T-wave abnormalities were observed. ST-segment depression was seen significantly more often in subjects >55 years of age (RR = 1.4) who were women (RR = 1.3) or nonwhite (RR = 1.5), were hypertensive (RR = 1.8), had diabetes mellitus (RR = 1.6) or who smoked cigarettes (RR = 1.5). Angiographic findings related to presence of ST-T-wave abnormalities included severe coronary obstruction (<70%), higher number of diseased vessels, and the presence of obstruction in the left anterior descending coronary artery. In a multivariate model, the most significant correlates of ST-T-wave abnormalities were presence of left ventricular contraction abnormality, followed by age, gender, presence of left anterior descending coronary artery disease, elevated end-systolic volume index, and a diagnosis of hypertension. Thus, electrocardiographic ST-T abnormalities has specific and significant clinical and pathophysiologic correlates.

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ST-segment and T-wave abnormalities are common. In the Framingham study, for example, ST-T changes were detected in 8.5% of men and in 7.7% of women,[1] whereas in a study of over 18,000 male civil servants reported by Rose et al,[2] ST depression was noted in 2.6% of those aged 60 to 64 years. These electrocardiographic changes have been associated with increased risks of death and morbidity from coronary artery disease in subjects without as well as with documented heart disease.[1,3–9] Because of this relation, others have sought to identify the clinical and risk factor correlates of electrocardiographic changes. Parameters associated with ST-T-wave abnormalities have included increasing age, female gender, elevated blood pressure, glucose intolerance, elevated cholesterol and cigarette abuse.[1,2,10] Many of these factors are also known to promote atherosclerosis.[11] The resultant coronary obstruction could then produce myocardial ischemia or necrosis that might, in turn, generate the electrocardiographic abnormality. However, little data are available directly relating the occurrence of resting ST-T-wave abnormalities to the underlying coronary pathoanatomy and pathophysiology. It was the specific goal of this study to explore this relation in a large cohort of subjects undergoing cardiac catheterization.

METHODS

The study population was selected from 18,958 patients undergoing cardiac catheterization at the Baptist Memorial Hospital from 1976 to 1986. Results were interpreted by experienced staff cardiologists to determine the presence, location and severity of coronary artery obstructions and to measure standard hemodynamic and functional variables.

Coronary lesions were considered significant if the obstruction was ≥70% (or 50% of the left main coronary artery); less severe (<70%) lesions were categorized as "mild" obstruction. Ventricular volumes were computed from single-plane angiograms after injection of contrast material into the left ventricle; a left ventricular contraction abnormality was diagnosed if hypokinesia or akinesia was detected in ≥1 of 8 left ventricular segments. Electrocardiograms were interpreted by computer (Marquette Electronics) and over read by staff cardiologists; an ST-T-wave abnormality was diagnosed if ST depression (≤ -100 uV), abnormal T-wave inversion, or both, were present on the electrocardiogram recorded immediately preceding catheterization.

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TABLE I Clinical Characteristics of Patients With and Without ST-Segment Abnormalities

Characteristic	No. of Pts.	% with Abnormal ST-Segment	p	Relative Risk (CI)*
All subjects	9,801	44.3		
Age <55 years	4,278	39.7	<0.001	1.4
Age ≥55 years	5,523	47.8		(1.3–1.5)
Men	6,237	41.8	<0.001	1.3
Women	3,564	48.5		(1.2–1.4)
White	8,682	43.1	<0.001	1.5
Nonwhite	1,119	53.4		(1.3–1.7)
Nonhypertensive	5,888	38.4	<0.001	1.8
Hypertensive	3,913	53.1		(1.7–2.0)
Nondiabetic	8,743	43.0	<0.001	1.6
Diabetic	1,058	54.6		(1.4–1.8)
NL cholesterol	5,116	51.1	0.652	
Elev. cholesterol	2,562	53.0		
Nonsmoker	4,210	38.8	<0.001	1.5
Smoker	5,591	48.4		(1.4–1.6)

* Relative risk of having an ST-T-wave abnormality with 1 alternative for each characteristic than with the other. All categories with lower confidence limits of >1.0 were statistically significant.

CI = Confidence interval; Elev. = elevated; NL = normal.

TABLE II Angiographic Patterns of Patients With and Without ST-Segment Abnormalities

Pattern	No. of Pts.	% with Abnormal ST-Segment	Relative Risk (CI)*
No CAD	2,511	32.4	1.0
Mild CAD	1,759	41.0	1.5 (1.3–1.7)
Severe CAD	5,531	50.7	2.1 (1.9–2.4)
Single coronary artery	2,081	47.9	
Left anterior descending	1,138	51.1	2.2 (1.9–2.5)
Left circumflex	361	42.7	1.6 (1.2–1.9)
Right	582	44.7	1.7 (1.4–2.0)
2-Vessel	1,692	50.5	
LAD + LC	621	51.2	2.2 (1.8–2.6)
LAD + Right	717	52.3	2.3 (1.9–2.7)
LC + Right	354	45.5	1.7 (1.4–2.2)
3-Vessel	1,233	54.8	2.5 (2.2–2.9)
Left main disease	525	53.1	2.4 (2.0–2.9)

* Relative risk of having ST-T abnormality compared to subject without coronary artery disease. All categories with a lower confidence limit of ≥1.0 were statistically significant.

CAD = coronary artery disease; CI = confidence interval; Mild CAD = <70% obstruction of any major epicardial artery; severe CAD = ≥70% obstruction of any major epicardial artery or ≥50% obstruction of left main artery; LAD = left anterior descending artery; LC = left circumflex artery.

Clinical, angiographic, hemodynamic and electrocardiographic data were prospectively entered into a computerized data base for analysis. Patients with the following conditions were excluded: (1) congenital, significant valvular or primary myocardial disease; (2) history of prior cardiac surgery; (3) unstable angina pectoris or acute myocardial infarction on the same admission as cardiac catheterization; and (4) bundle branch or left posterior fascicular block, Wolff-Parkinson-White syndrome, Q-wave myocardial infarction or paced rhythm. After these patients were removed, 9,801 cases remained for study.

Risk factor information for these patients was determined from the clinical record. Factors examined included history of diabetes mellitus, history of systemic hypertension, history of smoking and elevated plasma total cholesterol. Patients were defined as hypertensive if they were receiving antihypertensive medication or had a history of systemic arterial blood pressure >160/90 mm Hg. Hypercholesterolemia was defined as a plasma total cholesterol of ≥240 mg %. A diabetic was defined as a patient with a history of diabetes mellitus or treatment of hyperglycemia.

For each clinical, hemodynamic or angiographic variable, the relative risk (RR) of having an ST-T abnormality with than without the factor (e.g., hypertensive versus nonhypertensive) was computed, along with the 99% confidence interval (CI). If the CI did not cross unity, the increased risk of ST-T abnormality with an abnormality was statistically significant.

Analysis of the independent contribution of each of multiple parameters to the occurrence of ST-T abnormalities was assessed using a stepwise multiple linear regression model. The dependent variable was the presence or absence of an ST-T abnormality; independent variables were added or deleted from the model at each step based on the resultant reduction in variance ($p < 0.01$ to enter).

RESULTS

Clinical features of the 9,801 patients are described in Table I; 63.6% were men, 88.6% were white, and the average age was 56 years (mean ± standard deviation 11.4). Hypertension, diabetes and hypercholesterolemia were found in 39.9, 10.8 and 26.1%, respectively, whereas a history of cigarette abuse was found in 57.0%.

Univariate correlates of ST-T abnormalities: An ST-T abnormality was detected in 44.3% of all subjects, and was significantly more prevalent in older patients, women and nonwhite subjects than in those <55 years of age, men and whites. ST-T abnormalities were also more common in smokers and in those with diabetes or hypertension. In contrast, an elevated total cholesterol did not significantly increase the likelihood of exhibiting an ST-T-wave abnormality.

Angiographic correlates of ST-T-wave patterns are listed in Table II and graphically depicted in Figure 1. More patients with significant coronary disease had ST-T abnormalities than did those with mild disease, whereas those with mild disease were more likely to have abnormalities than were those with normal vessels. Similarly, the likelihood of having ST-T abnormality increased with increasing number of vessels obstructed.

Within subsets of patients with either 1- or 2-vessel disease, the presence of a significant obstruction in the left anterior descending artery increased the prevalence of ST-T abnormalities (Table II, Figure 2). In patients with 1-vessel disease, a significantly higher percentage of patients with an anterior descending lesion had ST-T abnormalities than did those with either a circumflex (RR = 1.4, CI = 1.1–1.8) or right (RR = 1.3, CI = 1.1–1.6) coronary lesion. In subgroups with 2-vessel disease, those with an anterior descending lesion in combination with a right coronary lesion had a higher likelihood of ST-T abnormality than did those with circumflex plus right coronary lesions (RR = 1.3, CI = 1.0–1.7). Those with anterior descending plus circumflex

TABLE III Hemodynamic Characteristics of Patients With and Without ST-Segment Abnormalities

Characteristic	No. of Pts.	% with Abnormal ST-Segment	Relative Risk (CI)
ESVI <34 ml/m^2	4,533	42.0	1.5 (1.3–1.6)
ESVI ≥34 ml/m^2	1,599	51.6	
EDVI <90 ml/m^2	5,105	42.7	1.3 (1.2–1.5)
EDVI ≥90 ml/m^2	1,849	49.4	
SVI <34 ml/m^2	2,942	45.4	1.1 (1.0–1.2)
SVI ≥34 ml/m^2	3,186	43.7	
EF ≥50%	7,679	43.8	
EF 31–49%	737	57.9	1.8 (1.5–2.1)
EF <30%	94	52.1	1.4 (0.9–2.1)
LVEDP <15 mm Hg	6,496	43.4	1.3 (1.2–1.5)
LVEDP ≥15 mm Hg	2,584	50.7	
Normal LV contraction	6,362	38.9	1.9 (1.7–2.0)
Abnormal LV contraction	3,439	54.2	

CI = confidence interval; EDVI = left ventricular end-diastolic volume; EF = left ventricular ejection fraction; ESVI = left ventricular end-systolic volume index; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; SVI = stroke volume index.

obstruction also had a higher incidence of ST-T abnormalities than did those with circumflex plus right coronary artery abnormalities, although the difference was not significant (p = 0.06).

The prevalence of ST-T abnormalities in patients with 3-vessel disease was compared to that with other patterns. The prevalence was not significantly higher than in those with anterior descending lesions alone (RR = 1.2, CI = 0.8–1.4) or in combination with either circumflex (RR = 1.2, CI = 0.9–1.4) or right (RR = 1.1, CI = 0.9–1.3) coronary artery obstructions. However, the prevalence was significantly higher than in those with right plus circumflex lesions (RR = 1.5, CI = 1.2–1.8).

Functional abnormalities are listed in Table III. ST-T abnormalities were more common in subjects with abnormal left ventricular contraction, elevated left ventricular end-diastolic pressure, reduced ejection fraction, or increased end-systolic or end-diastolic ventricular volume indexes.

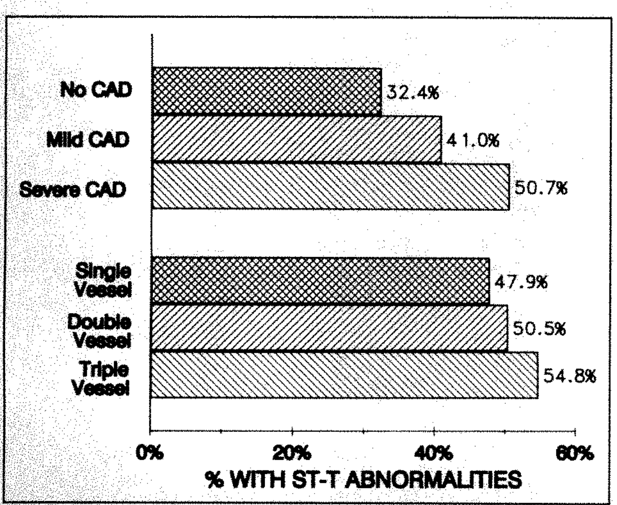

FIGURE 1. Prevalence of ST-T abnormalities in patients without coronary artery disease (CAD), with mild and with severe 1-, 2- or 3-vessel obstructions. Likelihood of ST-T abnormalities increased with increasing severity of coronary artery disease.

TABLE IV Stepwise Multiple Linear Regression Model of Factors Predicting ST-T-Wave Pattern

Step	Factor	Standardized Coefficient	p*
1	Abnormal LV contraction	0.52	<0.0001
2	Age	0.22	<0.0001
3	Gender	0.47	<0.0001
4	LAD narrowing	0.35	<0.0001
5	End-systolic volume index	0.37	<0.0001
6	Systemic hypertension	0.23	<0.001

* Significance of F test to remove from the model.
LAD = left anterior descending coronary artery; LV = left ventricular.

Multivariate correlates of ST-T abnormalities: Stepwise regression analysis was performed to determine which of these clinical and pathophysiologic variables were significant independent predictors of an abnormal ST-T wave (Table IV). Independent variables included clinical (age, race, gender), risk factor (systemic hypertension, hypercholesterolemia, diabetes mellitus, smoking history), angiographic (presence or absence of anterior descending, circumflex, right, or left main coronary artery lesions) and functional (end-systolic and end-diastolic volume indexes, ejection fraction, and presence of abnormal left ventricular contraction pattern) parameters. For this analysis, cases with mild stenoses (<70%) were excluded.

Of these variables, 6 were determined to have statistically significant, independent value in predicting the presence of ST-T abnormalities. The most significant predictor was the presence or absence of a left ventricular contraction abnormality. This single measure produced a sensitivity of 54%, a specificity of 61%, a positive predictive value of 43% and a negative predictive value of 71%.

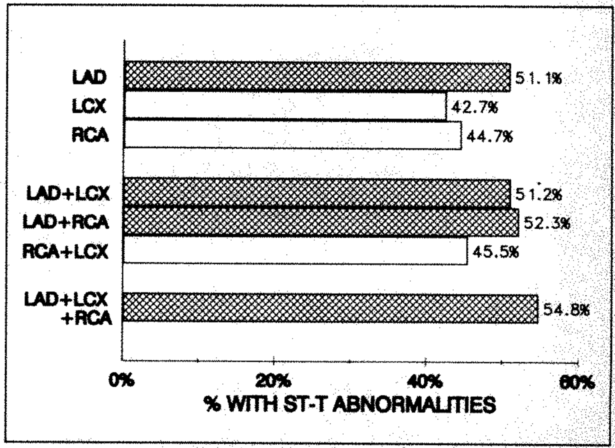

FIGURE 2. Prevalence of ST-T abnormalities in subsets with severe 1-, 2- and 3-vessel disease. The presence of significant disease in the left anterior descending artery (LAD), whether in 1- or 2-vessel disease subsets, increased the likelihood of ST-T changes. LCX = left circumflex artery; RCA = right coronary artery.

The other 5 significant variables included age, gender, presence of disease in the left anterior descending coronary artery, end-systolic volume index, and diagnosis of systemic hypertension. When these 6 variables were used, an accurate classification of 60.4% of cases, with a sensitivity of 59.4% and an specificity of 61.4%, was permitted.

The multivariate model was reconstructed after exclusion of 745 patients with an electrocardiographic diagnosis of left ventricular hypertrophy. Diagnosis of left ventricular hypertrophy was made by a point score technique based on precordial lead QRS amplitudes adjusted for age or limb lead amplitudes (R in lead I >1,300 μV or R in lead aVL >1,100 μV). The stepwise regression procedure again selected 6 variables as significant independent predictors of ST-T abnormalities ($p < 0.0001$). Five—left anterior artery disease, age, gender, presence of contraction abnormalities and history of hypertension—were the same as when patients with left ventricular hypertrophy were included. However, end-systolic volume index abnormalities was not selected and end-diastolic volume index was chosen.

DISCUSSION

The ST-T wave is generated, during sinus rhythm, by transmural differences in the repolarization properties of the ventricles.[12,13] Under normal conditions, endocardial action potentials are of longer duration than are epicardial ones, so that recovery of the outer wall precedes that of the inner wall. Extracellular systolic current then flows toward the epicardium resulting in the normally positive ST-T wave.

This normal gradient is perturbed by ischemia.[14,15] One electrophysiologic effect of ischemia is to shorten the duration of the action potential. Because ischemia tends to be more severe in the endocardial than epicardial layers,[16,17] action potentials in the inner wall become shorter than those near the epicardium. This reversal of the normal systolic transmural recovery gradient generates depressed ST segments and T-wave inversions. Diastolic injury currents, generated by reduced resting potentials in ischemic areas and directed away from the endocardium, likewise contribute to ST depression.[14,18]

Previous reports have described a higher incidence of ischemic events during follow-up of patients with than without ST-T shifts.[1-9] The worse prognosis is commonly considered to reflect extensive coronary disease.[6,7] Reported studies have provided some direct evidence that ST abnormalities do relate to more extensive disease; Humphries et al[7] reported higher angiographic scores in those with than without ST-T-wave abnormalities. However, it is also known that extensive coronary disease can exist with a normal electrocardiogram.[19]

Other studies have described the clinical and angiographic correlates of transient ST-T-wave abnormalities in patients with unstable angina pectoris. Most have reported a high prevalence of extensive coronary disease[20,21]; such patients may be expected to have more severe disease and poorer left ventricular function than do those with transient ST elevation.[21-23] In addition, inverted T waves identify a subset with more 3-vessel and left main coronary artery disease than do upright T waves.[24]

Clinical factors: Increasing age, cigarette smoking, glucose intolerance and hypertension all predispose to coronary atherosclerosis and thus may be anticipated to increase the likelihood of ST-T changes (Table I). Previous studies have similarly identified these variables.[1,2,10] For example, Rose et al[2] detected ST depression in 0.71% of men aged 40 to 49 years but in 2.64% of those aged 60 to 64 years.

An increased prevalence in women has also been described by some[10] but not all[1] observers. In a report by Liao et al,[10] the prevalence of ST-T abnormalities was greater in women than in men, possibly related to findings that autonomic imbalance occurred more frequently, ischemia was seen without coronary atherosclerosis, and so forth. The higher prevalence in nonwhites may relate to a higher prevalence of other risk factors (e.g., hypertension), or to the same but unknown factors that increase the likelihood of the so-called "juvenile T-wave" pattern in these groups.[25]

Angiographic patterns: Angiographic factors were consistent with the hypothesis that the prevalence of ST-T abnormalities increases with increasing ischemia.[6,7] Thus, the prevalence increased with the degree (mild versus severe) and extent (number of vessels) of obstruction.

A significant percentage of patients with ST-T abnormalities had only mild coronary disease or no disease. This was true even in this population referred for catheterization and who, presumably, had a high a priori risk of having ischemic disease. When viewed in the context of Baye's theorem, these data would then suggest that in patients not considered clinically to be at high risk for significant disease, the electrocardiographic finding may have a low predictive accuracy.

The second new finding of this study is the prominent increase in the prevalence of ST-T changes with significant anterior descending artery disease, whether in 1- or in 2-vessel disease patterns. Indeed, presence of isolated anterior descending disease was associated with as much ST-T abnormality as was 3-vessel disease. The significance of anterior descending disease was likewise supported by multivariate analysis; the presence or absence of an anterior descending lesion was 1 of 6 important variables associated with ST-T abnormalities.

The special importance of obstruction in the anterior descending artery is consonant with prior clinical data. de Zwaan et al[26,27] reported that, in patients with unstable angina, the presence of ST-T abnormalities in leads V_2 and V_3 is indicative of an anterior descending lesion. In all of 180 patients with this electrocardiographic pattern, the anterior descending artery was obstructed and in 75 the anterior descending lesion was the only abnormality.[27] In another report by Haines et al,[28] new anterior T-wave inversion during unstable angina had 80% predictive accuracy for anterior descending coronary artery disease. False-negative exercise test results are also seen less frequently in patients with isolated anterior descending disease than in those with circumflex or right coronary artery obstructions,[29-31] and development of marked ST depression during exercise is more common with anterior descending disease.[32]

Animal studies have also suggested that less ischemia in the anterior descending bed is needed to produce ST-T abnormalities than in the circumflex bed and, for a given degree of ischemia, the magnitude of ST depression is greater for anterior descending than for circumflex obstructions.[17] Total occlusion of the anterior descending artery in the dog also produces more extensive infarction than does occlusion of the circumflex artery,[33] whereas reductions in flow in that vessel result in more severe reduction in left ventricular function than do decreases in circumflex flow.[34]

Thus, lesions in the left anterior descending artery produce greater functional derangements in a variety of settings. Biophysical explanations center around the location of the anterior descending bed within the thorax. The more eccentric position of the perfusion bed within the chest reduces the distance from the ischemic zone to the recording electrodes on the chest wall, increasing the relative strength of the sensed electrocardiographic events. The anterior location of the affected perfusion bed results in ST-T abnormalities that would be projected to the anterior chest wall (i.e., the region from which cardiac potentials are regularly recorded). In contrast, potentials from lateral or posterior areas would project to torso regions not routinely sampled.

Physiologic explanations focus on functional differences between the coronary perfusion territories. Collateral resistance is higher[35] and flow lower[36] to the anterior descending than to other beds, decreasing the physiologic compensation for a lesion in the native vessel. Increased sensitivity to α-adrenergic stimulation in the anterior bed may further reduce flow.[37]

Functional abnormalities: The presence or absence of a left ventricular contraction abnormality was the first variable entered into the multivariate model. However, a significant number of patients without ST-T changes did have abnormal contraction patterns. This finding is also in agreement with those of prior studies. For example, Hilsenrath et al[38] reported a significant prevalence (34%) of asynergy in patients with normal QRS but abnormal T-wave patterns, and a lower (28%) but still significant prevalence if QRS and T waves were normal. Lindvall and Rehnqvist[39] reported no relation between ST patterns and ventricular function ≥10 days after infarction. Swartz et al,[40] however, found normal contractile patterns in 52 of 55 patients with normal electrocardiograms, and O'Keefe et al[41] reported normal ejection fractions in 95% of patients without ST-T-wave abnormalities.

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Changes in Diameter of Coronary Narrowings and Translesional Hemodynamics After Intracoronary Nitroglycerin

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The effect of intracoronary nitroglycerin on coronary stenosis dimensions and translesional hemodynamics was evaluated in 38 subjects (74 stenoses) referred for diagnostic coronary arteriography. Quantitative coronary arteriography was performed with standard Newtonian fluid dynamic equations used to estimate transstenotic gradients. Since intracoronary nitroglycerin can induce significant myocardial hyperemia (increased flow velocity), with increased translesional pressure gradients and a decrease in distal intraluminal pressure, the potential effect on subendocardial flow distribution was also analyzed. Minimum stenotic diameter significantly increased postnitroglycerin (NTG) (preNTG 1.42 vs postNTG 1.82 mm, $p < 0.01$), with a decrease in relative percent diameter stenosis (preNTG 45.7 vs postNTG 40.7%, $p < 0.05$). When changes in minimum stenotic diameter were analyzed according to stenosis severity (quartiles), the greatest effect was noted in those lesions with the least severe stenosis (quartile no. 1, 0.49 vs quartile no. 4, 0.32 mm, $p < 0.05$). If coronary blood flow velocity remains at baseline values (4 cm/s), intracoronary nitroglycerin was predicted to significantly decrease transstenotic pressure gradients (preNTG 1.01 vs postNTG 0.82 mm Hg, $p < 0.05$), with the greatest change shown in severe lesions (quartile no. 4, preNTG 3.79 to postNTG 2.28 mm Hg, $p < 0.01$). Accelerated coronary flow velocity (myocardial hyperemia) increased calculated translesional pressure gradients (4 cm/s, 0.82 mm Hg vs 20 cm/s, 8.00 mm Hg, $p < 0.01$), despite simultaneous stenotic vasodilation. Hemodynamic obstruction was particularly dependent on coronary flow velocity in the most severe stenoses (quartile no. 4, 4 cm/s, 2.28 vs 20 cm/s, 28.78 mm Hg, $p < 0.01$). Therefore, intracoronary nitroglycerin causes significant stenosis vasodilation, which under baseline (resting) conditions would partially alleviate hemodynamic obstruction. However, since this medication also produces transient increased coronary flow velocity (myocardial hyperemia), transstenotic pressure gradients may actually increase, with the potential for transmyocardial flow maldistribution and subendocardial ischemia.

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Nitroglycerin remains of fundamental importance in the treatment of acute myocardial ischemia. Despite continued debate as to its precise mode of action after systemic administration (decreased ventricular wall stress or increased coronary blood flow),[1,2] the advent of soluble formulations has expanded its usefulness within the cardiac catheterization laboratory. Nitroglycerin is commonly infused directly into the coronary arteries to improve "visualization" of distal vessels and to assess dynamic coronary tone.[3] Most commonly, however, intracoronary nitroglycerin is used to alleviate ongoing, acute myocardial ischemia in patients with critical coronary stenoses. Despite its universal application in this context, little information is currently available as to the quantitative effects of intracoronary nitroglycerin on coronary stenoses or its direct effect on transstenotic coronary hemodynamics. In addition, because relatively high doses (200 μgm) of intracoronary nitroglycerin can produce vasodilation of distal resistance vessels,[4,5] with increased coronary flow velocity (hyperemia) and greater transstenotic pressure gradients, possible changes in transmural flow distribution are discussed.

METHODS

Patient population: We studied 38 patients, 26 men and 12 women, with an average age of 57 years (range 36 to 73 years), referred for diagnostic coronary arteriography. A total of 74 proximal coronary stenoses were evaluated. Thirty-one stenotic segments were located in the left anterior descending coronary artery, 24 stenoses in the circumflex coronary artery, while 19 stenoses were in the right coronary artery. Subjects were excluded if presenting with an acute ischemic syndrome (unstable angina pectoris or myocardial infarction) or could not be withdrawn from sustained acting nitrates or calcium antagonists. The protocol was approved by the Committee for Research on Human Subjects (The Toronto Hospital).

Procedure: Cardiac catheterization was routinely performed in a postabsorptive state. All antianginal medications were discontinued for a minimum of 18 to 24 hours, with premedication consisting of oral diaze-

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pam (10 mg). No participant received atropine sulfate, while nitroglycerin was specifically avoided within 2 hours of the procedure. Multiangulated coronary arteriography was performed using nonionic contrast media (iohexol, 350 mgI/ml), and was preceded by a single, standard left ventriculogram (45 ml contrast media). Preliminary review of coronary anatomy via a videotape replay system allowed identification of stenoses suitable for quantitative coronary arteriography. Magnified coronary arteriography was provided by a 5-inch image intensifier, with minimization of pin-cushion distortion by precisely centering the stenosis within the radiographic field of view. While monitoring heart rate and systemic aortic pressure, coronary arteriography was repeated, using the projection that best delineated stenosis length and severity. Optimal coronary arterial opacification was achieved using a manual injection system. After observing a 5-minute stabilization period, intracoronary nitroglycerin was administered (total 200 μgm, concentration 40 μgm/ml) over 30 seconds, with repeat coronary opacification in an identical radiographic view. Subjects remained motionless throughout this interval, without alteration in image intensifier or table height to ensure constant magnification.

Quantitative coronary arteriography: A single radiographic frame was chosen for quantitative analysis.[6] This frame consisted of an optimally opacified segment during cardiac diastasis (diastole), with minimal motion artifact. To eliminate vessel foreshortening, the view showing the lesions' maximal length was selected. Kodak (8 × 11 inches) duplicating film was used to obtain a hard copy of this single frame and the luminal border was manually traced from the proximal "normal" to distal segment. These images were magnified (3×), and a center line with 1-mm perpendicular coordinates was generated using an image-processing computer (Kontron Cardio-200) and magnetic graphics tablet. Known dimensions of the angiographic catheter (Cordis number 8Fr) allowed calculation of a magnification factor and, thus, absolute stenosis dimensions. No correction for pin-cushion distortion was attempted because previous experience has shown minimal variance with the image intensifier (Optilux 27HD-Triplex, Siemens) used in this study.

Transstenotic fluid dynamic calculations: Based on classic Newtonian fluid dynamic equations previously published,[7,8] absolute stenoses dimensions were used to calculate translesional hemodynamics. These calculations presumed blood flow to be well developed and laminar in nature, because previous calculations of Reynold's number were markedly below the turbulent level (<1,200). Coronary stenosis resistance was considered to represent an integrated function of viscous interaction throughout the stenosis length and kinetic energy losses (separation) at the exit angle. For the purposes of calculation, absolute stenotic dimensions were converted to area by assuming a circular cross-sectional profile. The actual fluid dynamic equation for determining pressure loss (gradient) across stenoses is noted in the following formula: $\Delta \text{ pressure} = 8\pi \, \mu L/A_s{}^2 \times V(A_n) + p/2[1/A_s - 1/A_n]^2 \times [V(A_n)]^2$, where A_s = stenotic area, A_n = normal area, L = stenosis length and V = flow velocity.

Blood density (p) equalled 1.05 g/cm^3 with absolute values of blood viscosity (u) calculated using published data on the relation between red cell volume (hematocrit) and relative viscosity.[9] Baseline coronary flow velocities were assumed to equal 4 cm/s, which is a value consistent with measured flow velocities within our catheterization laboratory using a 20-MHz intracoronary Doppler velocity probe (Millar Instruments Inc.). Maximal coronary flow velocity was assumed to equal 20 cm/s (5 × baseline) and is similar to published data[10] in human subjects.

Statistics: Changes in minimum lumen diameter, percent diameter stenosis and calculated translesional

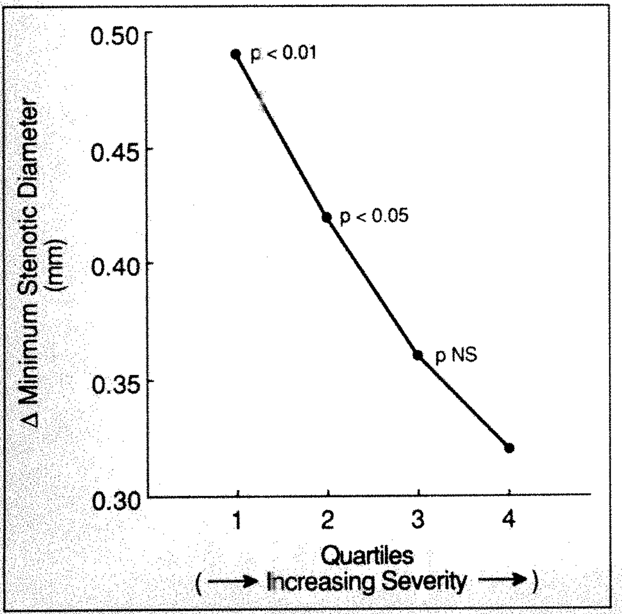

FIGURE 1. Changes in minimum stenotic diameter after intracoronary nitroglycerin, according to stenosis severity (quartiles). NS = not significant.

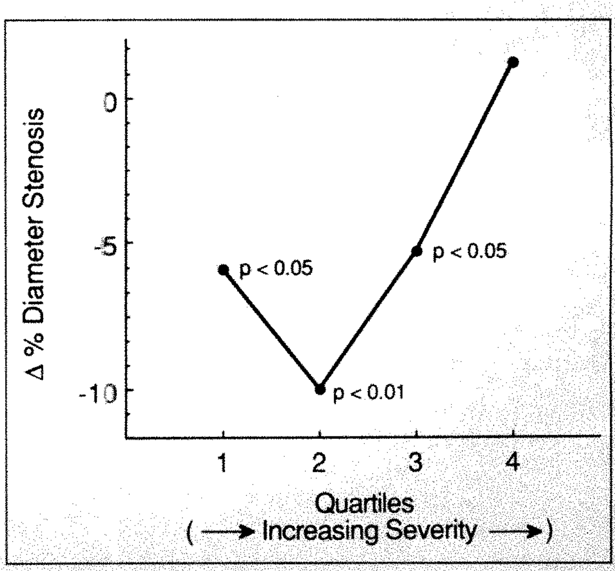

FIGURE 2. Changes in percent diameter stenosis after intracoronary nitroglycerin, according to stenosis severity (quartiles).

pressure gradients, for all stenotic segments analyzed ($n = 74$), are presented as mean values with standard deviations. To assess the influence of intracoronary nitroglycerin on lesions of differing hemodynamic severity, the entire group was divided into quartiles, based on minimum lumen diameter. Individual and group responses were compared using parametric statistics (*t* test) with rejection of the "null" hypothesis (groups equivalent) if $p < 0.05$.

RESULTS

Clinical: The study was well tolerated, with no adverse effects observed. Transient ST segment or repolarization abnormalities were commonly observed and were consistent with the intracoronary injection of radiographic contrast media. In the absence of precordial chest discomfort, these changes were not considered diagnostic of myocardial ischemia. Intracoronary nitroglycerin (NTG) resulted in a modest decrease in mean systemic aortic pressure (preNTG 103.0 vs postNTG 83.7 mm Hg, $p < 0.05$), with no changes in intrinsic heart rate (preNTG 64.2 vs postNTG 64.5 beats/min, difference not significant). No subject required an intervention (e.g., IV saline) for transient hypotension.

Quantitative arteriography: Considering all coronary stenoses ($n = 74$), the average minimum stenotic diameter equalled 1.42 ± 0.61 mm, with the entire group divided into equal quartiles of increasing severity based on minimum stenotic diameter (quartile no. 1, 2.25 ± 0.37, quartile no. 2, 1.61 ± 0.14, quartile no. 3, 1.12 ± 0.12 and quartile no. 4, 0.73 ± 0.13 mm). Intracoronary nitroglycerin significantly increased minimum stenotic diameter (preNTG 1.42 mm to postNTG 1.82 mm, $p < 0.01$), thus representing an absolute change equalling 0.39 mm. Figure 1 shows changes in minimum stenotic diameter, according to initial stenosis severity (quartiles). The greatest absolute changes were observed in subcritical stenoses; however, all coronary lesions responded to varying degrees. When vasodilation is expressed in relative terms, intracoronary nitroglycerin consistently decreased percent diameter stenosis (preNTG 45.7% vs postNTG 40.7%, $p < 0.05$). Figure 2 shows changes in relative percent stenosis after nitroglycerin as a function of initial severity. As might be anticipated, the greatest changes are noted in the least severe narrowings, while the most severe stenoses (quartile no. 4) actually showed a slight increase in relative obstruction (quartile no. 4, +1.12%). This apparent "increase" in stenosis severity is probably secondary to greater pharmacologic vasodilation in the "normal" reference segment of the proximal coronary artery.

Calculated transstenotic hemodynamics (baseline flow velocity): Figure 3 shows changes in calculated translesional pressure gradients, before and after intracoronary nitroglycerin. A significant decrease in transstenotic pressure gradient is predicted (preNTG 1.10 to postNTG 0.82 mm Hg, $p < 0.05$), thus representing a 25.4% decrease in the severity of hemodynamic obstruction. Figure 4 shows the resultant changes in transstenotic pressure gradient according to initial stenosis severity (quartiles). Intracoronary nitroglycerin failed to significantly alter translesional gradients within the 2 least severe categories (quartiles no. 1 and 2), while substantial decreases in pressure gradients were observed in the more severe lesions (quartile no. 3, 0.49 vs 0.35 mm Hg, $p < 0.01$ and quartile no. 4, 3.79 vs 2.28 mm Hg, both $p < 0.001$). Assuming baseline flow velocities are equal to 4 cm/s, this represents a modest absolute decrease in transstenotic pressure gradient equal to 0.14 mm Hg and 1.51 mm Hg, respectively.

Calculated transstenotic hemodynamics (increased flow velocity): Because transstenotic pressure gradients

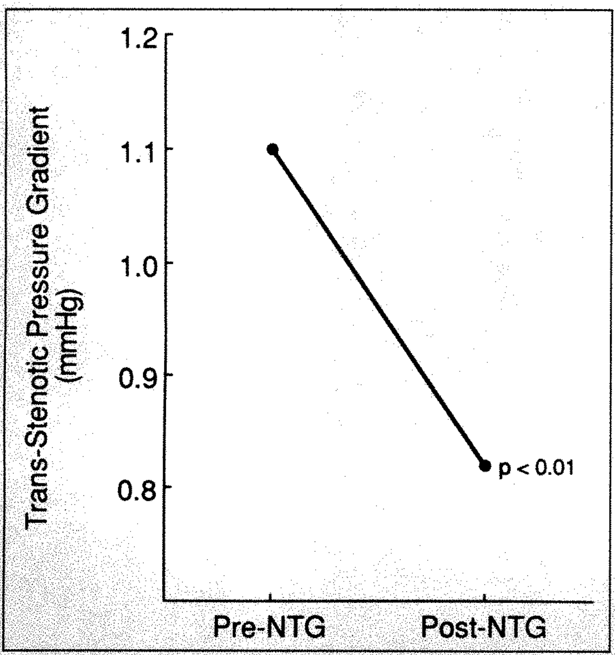

FIGURE 3. Transstenotic pressure gradients before and after intracoronary nitroglycerin assuming no increase in coronary flow velocity (4 cm/s). NTG = nitroglycerin.

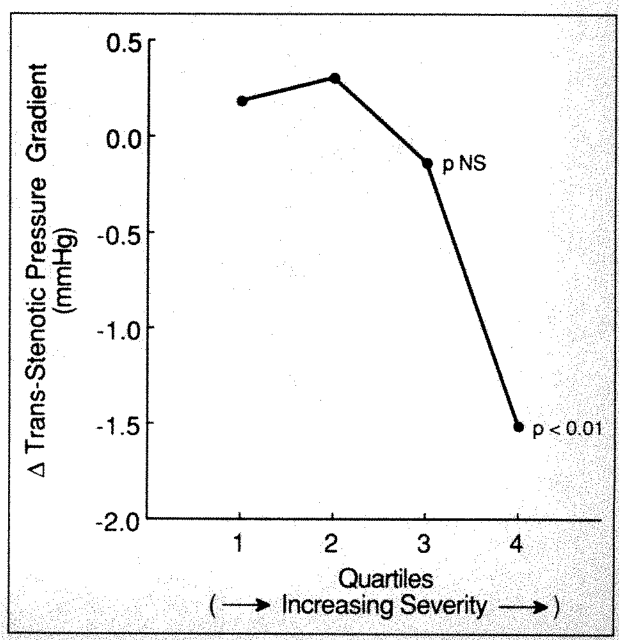

FIGURE 4. Changes in transstenotic pressure gradient after intracoronary nitroglycerin according to stenosis severity (quartiles) and assuming no change in coronary flow velocity (4 cm/s). NS = not significant.

are critically dependent on flow velocity, Figure 5 shows presumptive changes in translesional pressure differentials under a variety of hyperemic conditions (flow velocity 4 to 20 cm/s). Substantial transstenotic pressure gradients are predicted when coronary flow velocity approaches physiologic limits (5 × baseline). Figure 6 shows the relation between severity of coronary stenosis, as determined by minimum stenotic diameter and instantaneous flow velocity in the creation of translesional pressure gradients. Insignificant transstenotic pressure gradients are uniformly predicted if coronary flow velocity remains at baseline values (4 cm/s). However, as coronary flow velocity increases during nitroglycerin-induced myocardial hyperemia, a series of pressure curves can be generated suggesting exponential increases in transstenotic pressure gradient.

DISCUSSION

Quantitative changes after nitroglycerin: Previous studies with nitroglycerin, as administered by a variety of routes, have shown significant vasodilation of epicardial coronary arteries. In a study made up of 20 patients with coronary artery disease, Bachmann[11] observed a 15% increase in coronary diameters (2.40 to 2.56 mm) after oral nitroglycerin spray (0.8 mg). Rafflenbeul,[12] however, observed a variable response to sublingual isosorbide dinitrate (5 mg) with only some segments undergoing vasodilation. Methodologic difficulties, including the use of a vernier caliber measurement device to measure coronary dimensions, could have influenced these results. Feldman[13] analyzed the response to incremental dosages of intracoronary nitroglycerin and quantitated these changes according to location within the coronary vasculature. Maximum increases in coronary diameters occurred after 150 μgm and ranged from a 5% change within the left main stem vessel to a 34% increase in coronary diameter in the smaller, distal coronary arteries. Addressing the potential mechanisms of nitroglycerin action, Brown et al[14] evaluated quantitative changes in lumen cross-sectional area after both sublingual and intracoronary nitroglycerin. They observed a substantial increase in stenotic area (22 to 36%), with a significant decrease in calculated stenotic resistance (25 to 28%); although the magnitude of this effect was critically dependent on initial lesion severity. These investigators concluded that stenosis vasodilation by nitroglycerin was a major factor in the relief of myocardial ischemia. Moreyra[15] confirmed these results in a study designed to assess nitroglycerin tachyphylaxis. After graded dosages of intracoronary nitroglycerin, these workers noted a 20% increase in coronary diameter, with marked attenuation in subjects previously exposed to topical nitroglycerin.

Coronary stenosis hemodynamics: Although dynamic alterations in local vascular tone can have important effects on the degree of luminal narrowing, significant impairment of coronary blood flow ordinarily occurs only in the presence of a partially obstructive atherosclerotic plaque.[16] A hemodynamically obstructive lesion ("significant stenosis") will create a pressure differential (gradient) between the proximal and distal vasculature.[17] Baseline, resting coronary blood flow is maintained by an autoregulatory decrease in distal coronary vascular resistance.[18] This compensatory mechanism necessarily encroaches upon normal coronary hyperemic reserve and can limit maximal myocardial oxygen delivery during increased workloads (stress). Under these conditions, although volumetric coronary blood flow may be maintained, transmural maldistribution can occur, thus jeopardizing subendocardial viability.[19] Our data suggests substantial stenotic vasodilation by intracoronary nitroglycerin, with significant decreases in translesional pressure gradients. Although the absolute changes in minimum lumen diameter were less impressive in the most severe lesions (quartile no. 4), this

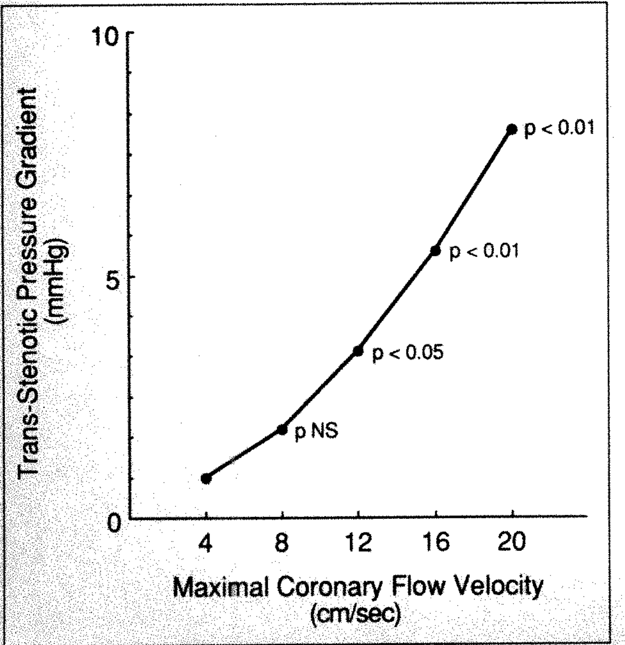

FIGURE 5. Transstenotic pressure gradient after intracoronary nitroglycerin as a function of coronary flow velocity (4 to 20 cm/s). NS = not significant.

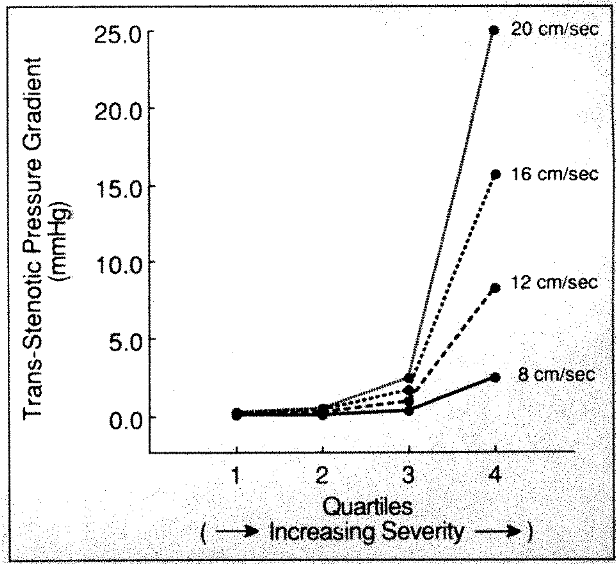

FIGURE 6. Transstenotic pressure gradient after intracoronary nitroglycerin as a function of stenosis severity (quartiles) and coronary flow velocity (8 to 20 cm/s).

group showed the greatest decrease in transstenotic pressure gradients. Since intracoronary nitroglycerin can produce transient myocardial hyperemia, the effect of increased coronary flow velocity was also evaluated. Particularly within the most severe stenoses, the obligatory increase in hemodynamic obstruction and decrease in distal intraluminal pressure could conceivably result in significant redistribution of myocardial blood flow. Previous studies, involving both animal models and actual subjects with coronary artery disease, would tend to support this hypothesis.

Myocardial blood flow after nitroglycerin: Fam and McGregor[20] studied the effect of intravenous nitroglycerin on canine regional coronary vascular resistance and directly compared these changes to intravenous dipyridamole. Substantial vasodilation was observed after both medications, with equivalent effects on distal resistance vessels and the induction of myocardial hyperemia. These findings were confirmed by Vatner,[21] who also noted significant initial vasodilation after systemic nitroglycerin (average coronary flow, +47 ml/min). A moderate decrease in systemic arterial pressure was also observed (−26 mm Hg), with subsequent autoregulated coronary vasoconstriction secondary to a decrease in myocardial oxygen requirements. The influence of systemic nitroglycerin on the transmural distribution of coronary blood flow, in the presence of a flow-limiting stenosis, was evaluated by Bache et al.[22] Under these conditions, subendocardial flow was already comprised, however, after the induction of myocardial hyperemia by transient coronary occlusion, these investigators noted a further redistribution of coronary flow away from the subendocardial territory. Forman[23] confirmed this response in an acute partial canine coronary occlusion model. The presence of a hemodynamically significant obstruction resulted in autoregulated vasodilation within the subendocardial resistance vessels and encroachment on subsequent hyperemic flow reserve. Intracoronary nitroglycerin preferentially increased coronary blood flow to the subepicardium at the expense (decreased flow) of the subendocardial region. In one of the few studies involving human subjects, Cohn et al[24] studied the effect of sublingual nitroglycerin on regional coronary flow distribution in 31 patients with coronary artery disease. Using a Xenon-133 washout technique, increased regional blood flow was directly correlated with the presence of angiographic collaterals. In their absence, regional myocardial blood flow failed to increase after nitroglycerin. "Steady-state" conditions were probably not achieved during this study, with further technical limitations precluding evaluation of the transmural distribution of myocardial blood flow. These data, however, may explain the findings by Ganz and Marcus[25] that intracoronary nitroglycerin failed to alleviate pacing-induced angina pectoris. In 25 subjects with coronary artery disease, coronary blood flow was evaluated using a thermodilution coronary sinus flow technique, with nitroglycerin producing a transient (26 seconds) hyperemic response. Despite this enhanced coronary blood flow, intracoronary nitroglycerin (75 μgm) did not alleviate chest discomfort, although sublingual nitroglycerin was often effective. It is conceivable that this lack of a beneficial response to intracoronary nitroglycerin was secondary to an unappreciated maldistribution in coronary blood flow within the subendocardial territory.

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Cycle-Length Response of Ventricular Tachycardia Associated with Coronary Artery Disease to Procainamide and Amiodarone

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We undertook this study to determine if the cycle-length response of ventricular tachycardia (VT) to procainamide and amiodarone is similar in the individual patient. We enrolled 40 patients with uniform, monomorphic VT at a baseline, drug-free electrophysiologic study, after procainamide infusion and during oral amiodarone therapy. We found a significant correlation ($p < 0.01$) between VT cycle-lengths on the 2 agents as well as the percent change in cycle length from baseline. Only 60% of the patients exhibited VT rates within 10% between the 2 agents. Importantly, <20% of patients had further slowing of the VT rate (>10% slowing) during amiodarone therapy as compared to procainamide. Thus, although the cycle-length response of VT to procainamide correlates with the cycle-length response to amiodarone, 40% of patients have a disparate response (>10% difference in cycle length) to the 2 agents; additional slowing of VT rates in response to amiodarone beyond that seen with procainamide is unlikely. These results have important implications regarding the institution of amiodarone therapy and the need for repeat electrophysiologic testing during amiodarone therapy.

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Procainamide and amiodarone are used frequently in the treatment of sustained ventricular tachycardia (VT). The effects of these agents on VT have been studied singly and in combination.[1–6] Both agents slow conduction and prolong refractoriness. It is also known that the mean prolongation of the VT cycle length with both drugs is similar.[1,6] However, whether the cycle-length response to 1 agent is similar to the response to the other in individual patients has not been addressed previously. The decision to institute amiodarone therapy is frequently made with the hope of either preventing VT induction[7] or producing greater prolongation of the VT cycle length.[8] However, most patients have persistent VT inducibility during amiodarone therapy.[7] This study examines whether the cycle-length response of sustained monomorphic VT to amiodarone therapy is similar to that occurring after procainamide infusion.

METHODS

We studied 41 patients with inducible sustained monomorphic VT. There were 35 men and 6 women aged 39 to 78 years (mean 62). All had documented coronary artery disease with previous myocardial infarction. Twenty-three patients presented with cardiac arrest or VT with loss of consciousness (poorly tolerated tachycardia), and 18 presented with hemodynamically tolerated VT. Forty patients had inducible monomorphic VT in the baseline state after procainamide infusion and during oral amiodarone therapy. One patient's VT was rendered noninducible by amiodarone and is excluded from analysis.

Antiarrhythmic agent administration: All patients underwent programmed stimulation in the baseline state after all antiarrhythmic medications had been stopped for at least 5 drug half-lives. The patients received a loading dose of procainamide of 15 mg/kg infused at a rate of 50 mg/min followed by a maintenance infusion of 4 to 8 mg/min during repeated stimulation. Blood samples were taken for serum procainamide determinations 5 minutes after the completion of the loading dose. Amiodarone was given as a loading dose of 1,400 mg/day × 7 days followed by maintenance therapy of 400 mg daily. Follow-up electrophysiologic testing was undertaken 12.7 ± 2.3 days after initiating amiodarone therapy.

Stimulation protocol: Our stimulation protocol has been described.[1] Briefly, single, double and triple extrastimuli are introduced during 2 paced cycle lengths of

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TABLE I Ventricular Tachycardia Cycle Lengths in All Patients

	Cycle Length		
	Identical Morphology	Fastest	First
Baseline	256 ± 25	247 ± 38	260 ± 35
Procainamide	320 ± 36	322 ± 51	333 ± 58
Amiodarone	328 ± 46	305 ± 44	316 ± 46

TABLE II Percent Change in Ventricular Tachycardia Cycle Length

	Identical Morphology (%)	Fastest (%)	First (%)
All Patients			
Procainamide	28	32	29
		p = 0.02	
Amiodarone	25	24	22
Patients with Poorly Tolerated Tachycardia			
Procainamide	26	27	23
Amiodarone	26	23	21
Patients with Well-Tolerated Tachycardia			
Procainamide	32	40	35
		p = 0.03	
Amiodarone	25	26	23

TABLE III Correlations (R Values) of Cycle Lengths and Percent Change from Baseline on Procainamide and Amiodarone

	CL on P vs CL on A	% change on P vs % change on A
All Patients		
Tachycardia		
Identical	0.72*	0.45†
Fastest	0.45‡	0.52‡
First	0.50*	0.30
Patients with Poorly Tolerated Tachycardia		
Tachycardia		
Identical (n = 20)	0.70*	0.55†
Fastest (n = 27)	0.47†	0.58‡
First (n = 27)	0.79*	0.70*
Patients with Well-Tolerated Tachycardia		
Tachycardia		
Identical (n = 9)	0.84‡	0.39
Fastest (n = 19)	0.42	0.58‡
First (n = 19)	0.22	0.00

* p <0.001; † p <0.05; ‡ p <0.01.
A = amiodarone; CL = cycle length; P = procainamide.

600 (or 550) and 400 ms from the right ventricular apex and the right ventricular outflow tract. All stimulation is performed at twice-diastolic threshold with a 1-ms pulse width. Recordings are made with a 16-channel physiologic recorder (VR 16, Electronics for Medicine) and real-time recordings made with an ink-jet recorder (Siemens Elema Mingograph) at paper speeds of 100 mm/s.

Data analysis: The cycle lengths of 5 VT cycles were averaged to obtain the VT cycle length. Morphology of the tachycardia was assessed from surface leads 1, 2, 3, V_1 and V_6 displayed on the recorder.

The cycle lengths of VT were compared in 3 ways. First, only those tachycardias exhibiting identical morphology during all 3 electrophysiologic studies were included. There were 24 such tachycardias in 22 patients. Second, the fastest VT encountered at each study was compared. Finally, the first VT induced at each study was compared.

Comparison of morphologically identical tachycardias provides insight into whether the effects of the 2 antiarrhythmic agents on the electrophysiologic substrate of a given VT circuit are similar. Comparison of the fastest VT at each study provides practical information that may be useful. The decision to maintain a specific pharmacologic agent is often based on whether the fastest VT induced during an electrophysiologic study appears to be hemodynamically tolerated. Comparison of the first VT encountered at each study is also provided because the practice of many electrophysiologists is to terminate the electrophysiologic study when sustained VT is first encountered, a practice we do not advocate.

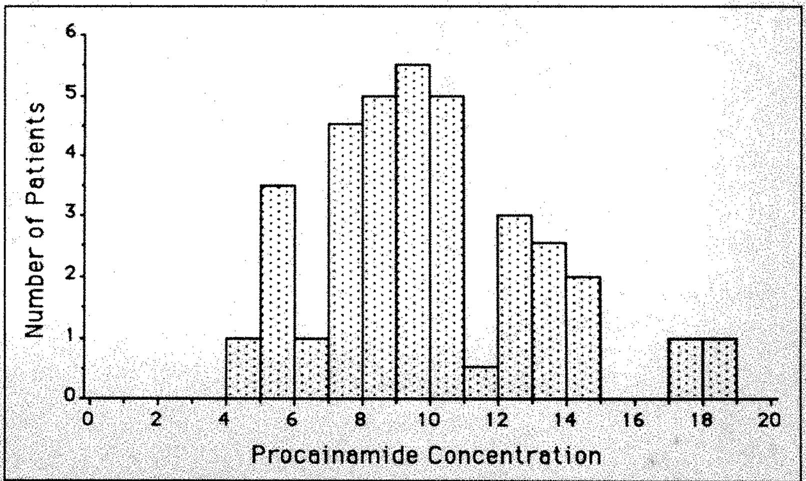

FIGURE 1. Distribution of serum procainamide concentrations (mg/liter) for the 40 patients.

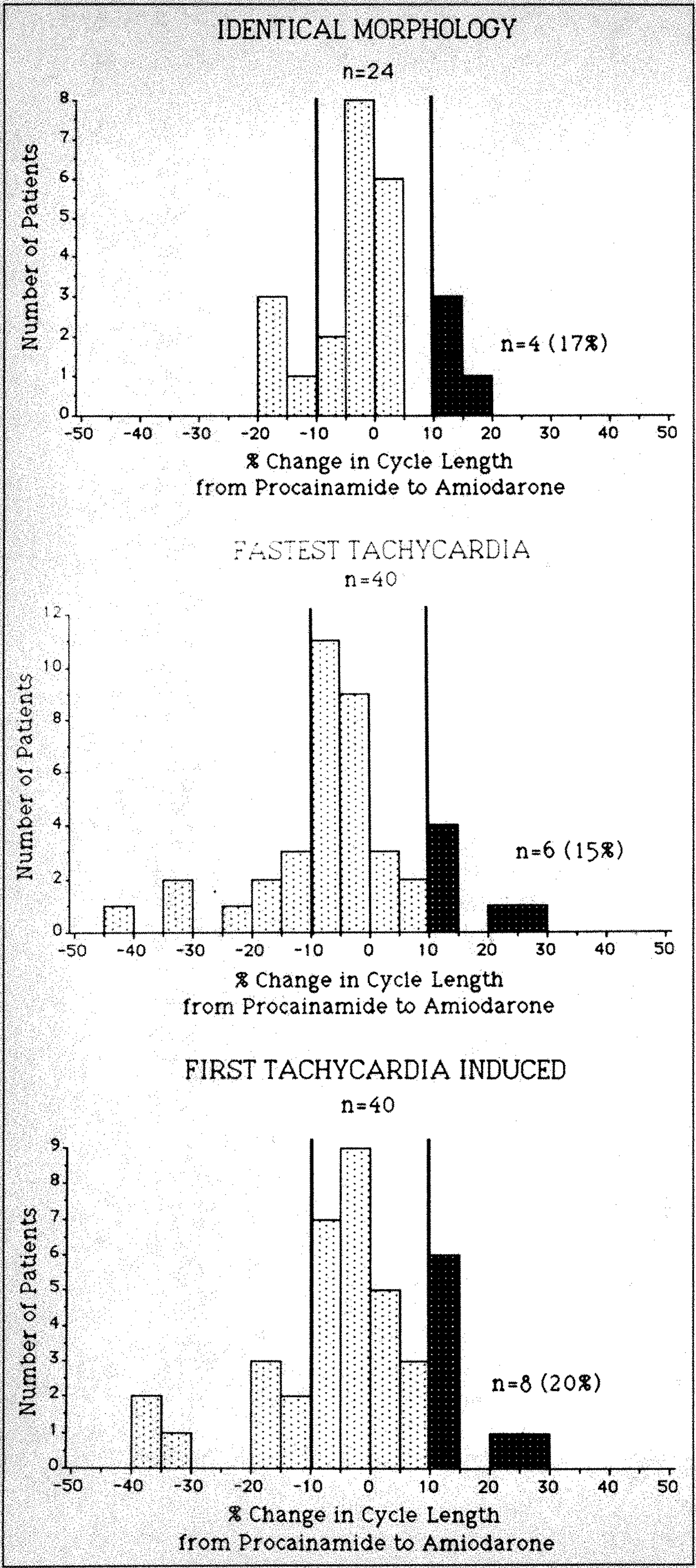

FIGURE 2. The percent difference in VT cycle length between procainamide and amiodarone therapy for VT of identical morphology *(top)*, fastest VT induced *(middle)* and first VT induced *(bottom)*. In each panel, the bold upright lines encompass those patients with a ≤10% difference in cycle length between the 2 therapeutic regimens. The *dark shading* indicates those patients whose VT rate was >10% slower on amiodarone as compared to procainamide and for each type of VT represents <20% of patients.

For comparing the cycle lengths of VT at baseline, after procainamide infusion and during amiodarone therapy, we used the *t* test for paired samples. The *t* test for unpaired samples was used to compare cycle-length changes in response to drugs between patients who had presented with tolerated VT with patients who presented with poorly tolerated VT. Linear regression analysis was used to assess the correlation of cycle length of VT after procainamide with the cycle length during amiodarone and the correlation of the percent change in VT cycle length from baseline to procainamide with the percent change from baseline to amiodarone.

RESULTS

The cycle lengths of VT for all patients are listed in Table I. There was no difference in baseline cycle length between patients who presented with poorly tolerated rhythms and those who presented with well-tolerated rhythms. Procainamide and amiodarone both prolonged VT cycle length from baseline for VT of identical morphology, fastest VT and the first VT induced at each study.

Table II lists the percent change in cycle length from baseline to procainamide and amiodarone. This data is presented for all patients, those who presented with poorly tolerated rhythms and those who presented with tolerated rhythms. There were no significant differences between these 2 subgroups of patients for any of the 3 categories of VT. There were significant differences between the response to procainamide and the response to amiodarone only when considering the fastest VT in all patients and in the subgroup with tolerated rhythms.

The distribution of serum procainamide concentrations is listed in Figure 1. The mean procainamide concentration was 9.9 ± 3.2 mg/liter. The procainamide concentration was not available in 2 patients.

There was a statistically significant correlation of the VT cycle length after procainamide infusion with the VT cycle length during amiodarone therapy (Table III). There was also a significant correlation of percent change in cycle length from the baseline study on procainamide with percent change from baseline on amiodarone. When we separate the patients according to their presentation, most of these correlations fail to reach significance in the group with tolerated rhythms.

Figure 2 shows the distribution of the percent change in VT cycle length from the study after procainamide infusion to that during amiodarone therapy. In approximately 60% of cases in each type of VT (16 of 24 [67%] of identical morphology VT, 23 of 40 [58%] of fastest VT and 23 of 40 [58%] of first VT), there was <10% difference in cycle length between the study on procainamide and the study on amiodarone. If we define a ≥10% change in cycle length as important, <20% of patients had greater slowing of the rate of VT during amiodarone therapy when compared to the effect of procainamide (Figure 2).

DISCUSSION

Antiarrhythmic drug therapy of sustained VT is undertaken primarily with the goal of rendering the VT noninducible. In the majority of patients, however, serial electrophysiologic studies fail to define an effective medical regimen.[9] If procainamide fails to suppress the inducibility of VT, other agents, including amiodarone, are unlikely to succeed.[7,8,10] In these patients, a secondary goal of slowing the VT is often pursued. Whether or not a VT is hemodynamically compromising is in large part determined by the tachycardia rate.[11] Previous studies have shown that the finding of only well-tolerated VT during electrophysiologic testing during amiodarone therapy identifies patients at low risk of catastrophic arrhythmia recurrences.[8]

Procainamide and amiodarone both prolong VT cycle length and thus offer the possibility of sufficiently slowing a poorly tolerated VT and rendering it hemodynamically well tolerated. The ability to predict the rate response of the VT to amiodarone therapy from the rate response to procainamide infusion would be clinically useful. In our series, we have shown that the cycle length of VT and the percent change in cycle length from baseline during amiodarone therapy correlates with these parameters following procainamide infusion. However, in only 60% of the patients the VT cycle length on amiodarone was within 10% of the cycle length on procainamide. In addition, <20% of patients had greater slowing (≥10% decrease in rate) of their VT with amiodarone as compared to procainamide.

Limitations: Our study assessed the ability to predict VT cycle length after a 1-week oral load of amiodarone from the response to an intravenous infusion of procainamide administered in the electrophysiology laboratory. Although the electrophysiologic effects of oral and intravenous procainamide are alike when similar serum concentrations are achieved, the cycle length of induced VT can differ in individual patients.[2] It has also been shown that during chronic amiodarone therapy, one can anticipate further slowing of the VT in comparison to that seen during short-term therapy.[12] We do not, however, have follow-up data during chronic amiodarone therapy in this group to assess whether their VT cycle lengths increase during chronic amiodarone therapy to approximate the cycle lengths observed after procainamide infusion. Also, we advise caution in extrapolating from our results to treatment regimens of procainamide and amiodarone that differ from those followed in this study. Finally, VT rate is only 1 factor in determining hemodynamic status during a tachycardia.[11] Our study did not address other factors that are relevant to this issue.

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Atrial Endocardial Mapping in the Rare Form of Atrial Flutter

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Endocardial atrial activation mapping was performed in 7 patients with rare atrial flutter (AF), inscribing predominantly positive deflections on leads II, III and aVF. In 2 cases both a rare and a common AF were mapped on different occasions. Every case displayed circular right atrial activation. In 5 of the 7 cases rare AF direction was clockwise (craniocaudal in the septum and posterior wall and caudocranial on the lateral and anterior walls). In 2 cases rare AF direction was counterclockwise (caudocranial in the septum and posterior wall and craniocaudal in the lateral and anterior walls). Both common AF rotated counterclockwise. A "line" of conduction delay or block was present in both clockwise and counterclockwise circuits between the posterior and lateral walls, in the probable location of the crista terminalis. This line of block extended the central obstacle made by the inferior vena cava toward, but perhaps not all the way to, the superior vena cava, making activation rotate roughly around the tricuspid ring. The ridge between the inferior vena cava and the tricuspid ring was a critical anatomic "closing" point in all clockwise and counterclockwise circuits. Right atrial macroreentry underlies rare AF. Direction of activation tends to be opposite to that in common AF. The cause of the positive deflection is unclear.

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Endocardial mapping of atrial flutter (AF) has shown atrial activation patterns compatible with large reentry circuits.[1-4] In common AF (predominantly negative deflections in leads II, III and aVF) right atrial activation follows a circular pattern, with caudocranial activation of the septum and craniocaudal activation of the lateral and anterior walls. Double-spike electrograms are usually recorded from the posterior or posterolateral walls, suggesting that slow conduction or block in this area supports the circuit.[3,4] Only a few atypical AFs seem to depend on left atrial circuit.[2,3] We report endocardial mapping of the rare form of AF, inscribing positive deflections on the inferior leads, that Puech called "rare."[1]

METHODS

Patients: We mapped 9 episodes of AF in 7 patients (Table I). Associated diseases were Wolff-Parkinson-White syndrome, surgically corrected atrial septal defect, ischemic heart disease with bypass surgery and left ventricular dilatation of unknown cause (1 each). Cardiac disease was absent in 3 cases. One patient (no. 4) was included in a previous report.[4]

Three patients received no cardioactive medications, 2 received quinidine (800 mg/day) and digoxin, 1 received quinidine (600 mg/day) and 1 propafenone (900 mg/day).

Definition of atrial flutter: AF was defined as an atrial tachycardia, without a stable baseline, at a rate between 250 and 300 cycles/min. It is difficult to define a positive versus negative deflection in a continuously waving pattern, and we relied on visual impressions and agreement among several investigators (Figures 1 and 2). The positive patterns are clearly different from the usual sawtooth pattern of common AF, but have different wave morphologies. In 2 cases (nos. 1 and 2; Figures 1 to 3) both rare and common AF were mapped. In case 2 rare AF changed to common AF after stimulation. In case 1 both patterns were precipitated by atrial stimulation on separate occasions.

Mapping technique: The endocardial mapping technique has previously been described.[3,4] Bipolar electrograms (50 to 600 Hz) were recorded by means of quadripolar electrode catheters with 0.5 to 1 cm separation. Siemens-Elema preamplifiers, amplifiers and recorder were used in 6 cases, and Electronics for Medicine (DR-12) amplifiers and recorder were used in 1 (case 4). AF stability was checked by simultaneous recording of 3 to 6 surface leads (I, II, III, V_1, V_2 and V_6 in 5 cases, leads I, II and III in 1 and Frank's orthogonal leads X, Y and Z in 1).

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TABLE I Summary of Clinical Features

Case	Age (yrs) & Sex	Heart Disease	Medication*	Flutter Type	Flutter CL	Flutter Rotation
1	28M	0	0	Rare	185	CW
				Common	200	CCW
2	73M	CAD, HBP	0	Rare	230	CW
				Common	230	CCW
3	55M	0	0	Rare	215	CCW
4	40M	WPW	Propafenone (900 mg)	Rare	290	CCW
5	52F	Operated ASD Left SVC, SH	Quin (600 mg)	Rare	270	CW
6	68M	COPD	Quin (800 mg) Digoxin	Rare	240	CW
7	82F	Parkinson's	Quin (800 mg) Digoxin	Rare	255	CW

* Doses indicated are per 24 hours.
ASD = atrial septal defect; CAD = coronary artery disease; CCW = counterclockwise; CL = cycle length (ms); COPD = chronic obstructive pulmonary disease; CW = clockwise; HBP = high blood pressure; LV = left ventricle; Quin = quinidine; SH = systemic hypertension; SVC = superior vena cava; WPW = Wolff-Parkinson-White syndrome.

Angling or biplane fluoroscopy was used to check catheter position. Superior and inferior vena cava and the tricuspid valve served as references. Catheters in the coronary sinus and right atrial appendage recorded fixed references. A third "exploring" catheter served to obtain sequential recordings from 3 to 5 levels of the septal, posteroseptal, posterior, posterolateral, lateral, anterolateral or anterior right atrial walls, in craniocaudal direction, between the superior and inferior venae cavae. The atrial "floor" around the inferior vena cava was mapped with a circular motion of a curved catheter, "hooked" in this area from the inferior vena cava.

Left atrial activation was recorded from the coronary sinus and/or pulmonary artery (high lateral left atrium), unless a patent foramen ovale was present, as in cases 2 and 5. During sequential coronary sinus or pulmonary artery mapping the right atrial appendage electrogram was used as fixed reference.

Measurements and map drawing: Local activation time was measured as the interval between the initial sharp deflection of the reference and local electrograms. Two activation times were noted for double spikes (Figure 3) at the onset of each spike (see maps in Figures 4 to 6). An arbitrary 0 point was assigned for composition of the map, looking for easy visual comprehension. For presentation of the endocardial maps we chose a schematic "wide-angle" view of both atria from the mitral and tricuspid rings (Figures 4 to 6) where septal, posterior and lateral right atrial walls are seen through the tricuspid valve, while the anterior wall is drawn "outside" the tricuspid ring from the epicardial side.

Ethical considerations: The study protocol was approved by the Hospital Research Committee. All patients gave informed consent for the procedures, which were an extension of a therapeutic intervention, aimed at AF interruption.

RESULTS

Maps included 14 to 33 points (Figures 4 to 6). Right atrial activation accounted for all the AF cycles,

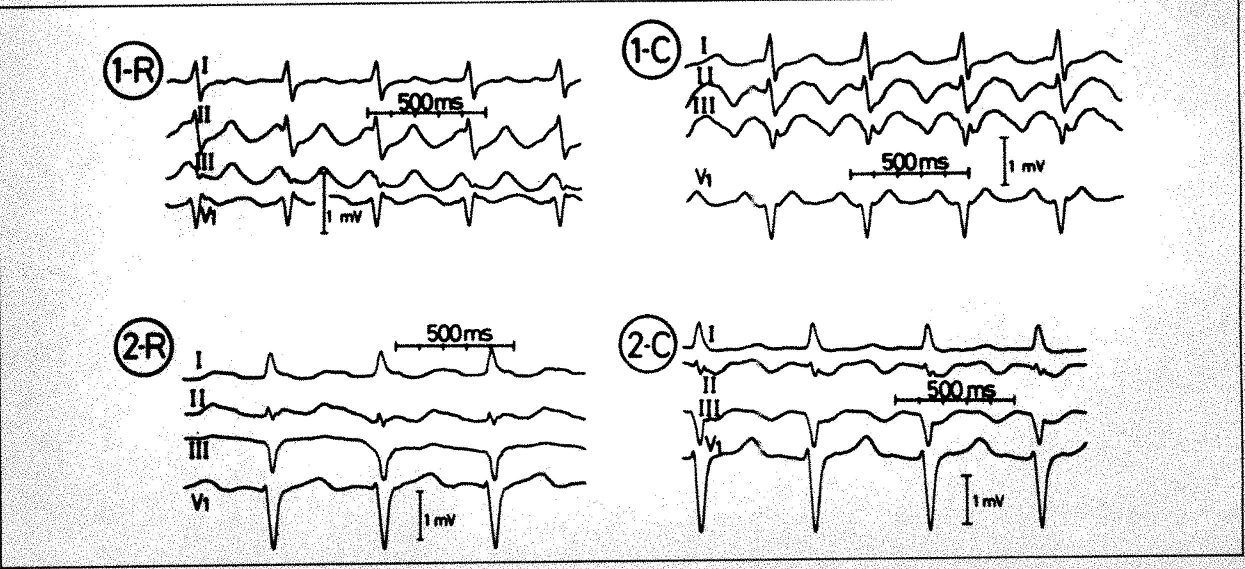

FIGURE 1. Electrocardiographic patterns of cases 1 (*top*) and 2 (*bottom*). C = common flutter. R = rare flutter.

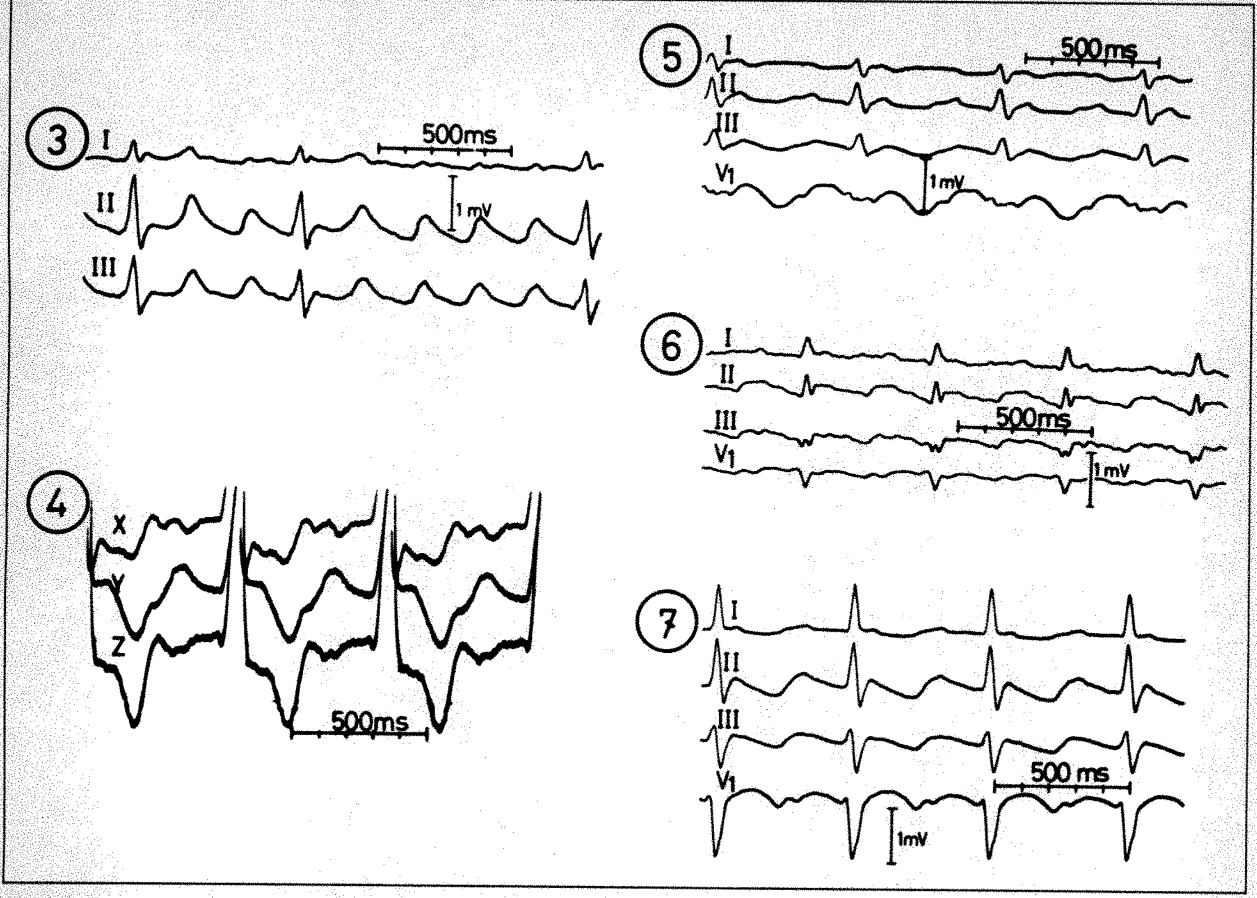

FIGURE 2. Electrocardiographic patterns of cases 3 to 7.

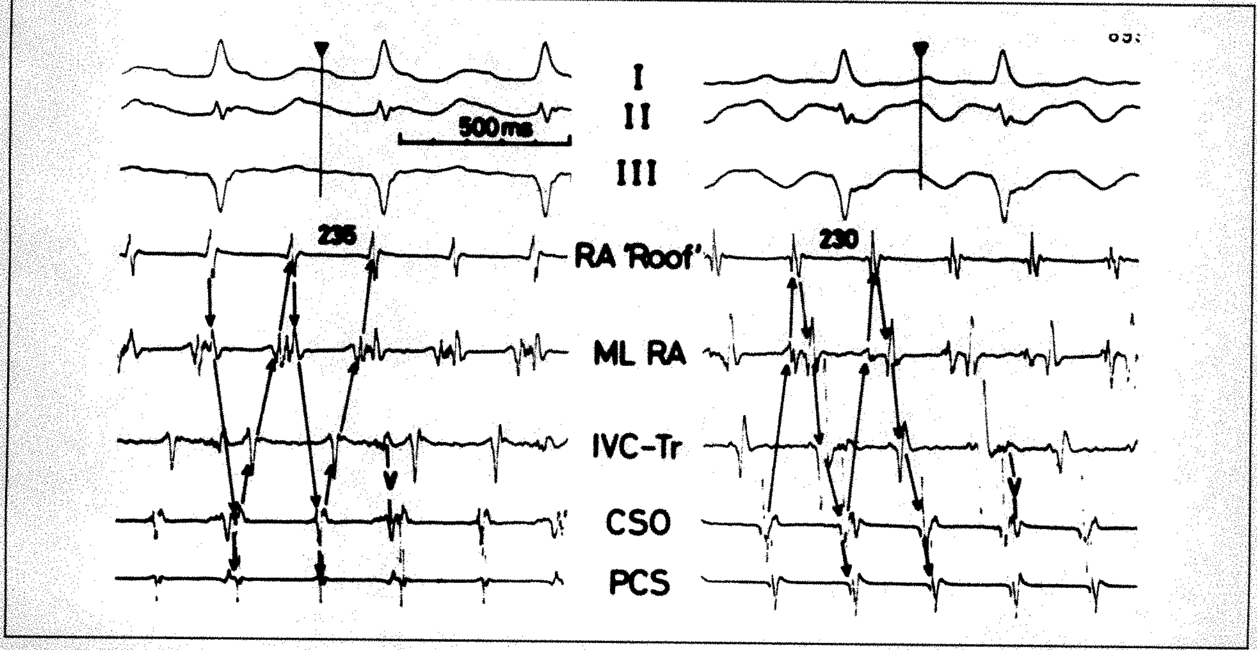

FIGURE 3. Case 2. Surface electrocardiogram and intracardiac recordings (*top to bottom*) from: high right atrium, anterior to the superior vena cava (RA "Roof"); midlateral right atrium (ML RA); inferior vena cava–tricuspid valve ridge (IVC-Tr); coronary sinus opening (CSO) and proximal coronary sinus (PCS). *Left panel,* recordings during rare atrial flutter; *Right panel,* after conversion to common flutter by stimulation. Only seconds separate both recordings (catheters remaining stable). Note the sequence change of IVC-Tr and CSO electrograms. The 2 spikes recorded at ML RA fit respectively in the ascending and descending arms of the activation circuit. The vertical line on the electrocardiogram marks the 0 reference taken for the maps (see Figure 4 [2-R and 2-C]).

with ≤60-ms gaps in all but cases 4 and 5. In these 2 cases no information was obtained from the right atrial floor, resulting in 130- and 115-ms gaps in the AF cycle. Left atrial data were obtained in 4 cases by deep penetration of the coronary sinus (cases 6 and 7) or via a patent foramen ovale (cases 2 and 5).

Activation in rare atrial flutter: Circular activation was always present in the right atrium with either of 2 patterns: (1) caudocranial activation of the anterior and lateral walls and craniocaudal activation of the septal and posterior walls (clockwise circuit) (cases 1, 2 and 5 to 7; Figures 4 and 6); (2) caudocranial activation of the septal and posterior walls and craniocaudal activation of the lateral and anterior walls (counterclockwise circuit) (cases 3 and 4; Figure 5). In the 5 maps with right atrial floor data, activation times from the inferior vena cava–tricuspid valve rim filled the gap between the activation of the anterior/lateral and posterior/septal walls, regardless of the direction of activation. When data from the left atrium were obtained, this did not seem to be an essential part of the activation circuit (cases 2 and 5 to 7; Figures 4 and 6).

No matter what the general rotation direction, activation of the posterior wall and the adjacent lateral wall was always in opposite directions. There was a high prevalence of double-spike electrograms in the posterolateral wall, and in some more detailed maps an entire craniocaudal "line" of double spikes was recorded in the posterolateral wall (cases 1, 6 and 7; Figures 4 and 6). The activation times of the 2 spikes tended to align with those of the adjacent posterior and anterior or lateral walls as if representing activation at both sides of a line of block.

Activation in common atrial flutter: Common AF in cases 1 and 2 showed counterclockwise circuits (Figure 4). The change from clockwise to counterclockwise rotation of case 2 is illustrated in Figure 3. In rare AF the onset of the positive wave in lead II coincided with high right atrial activation. In common AF activation of the low septal wall coincided with the onset of the negative deflection. There was no apparent difference in the activation velocity of the craniocaudal and caudocranial arms of activation, suggesting that localized conduction delay may be responsible for wave morphology. Avail-

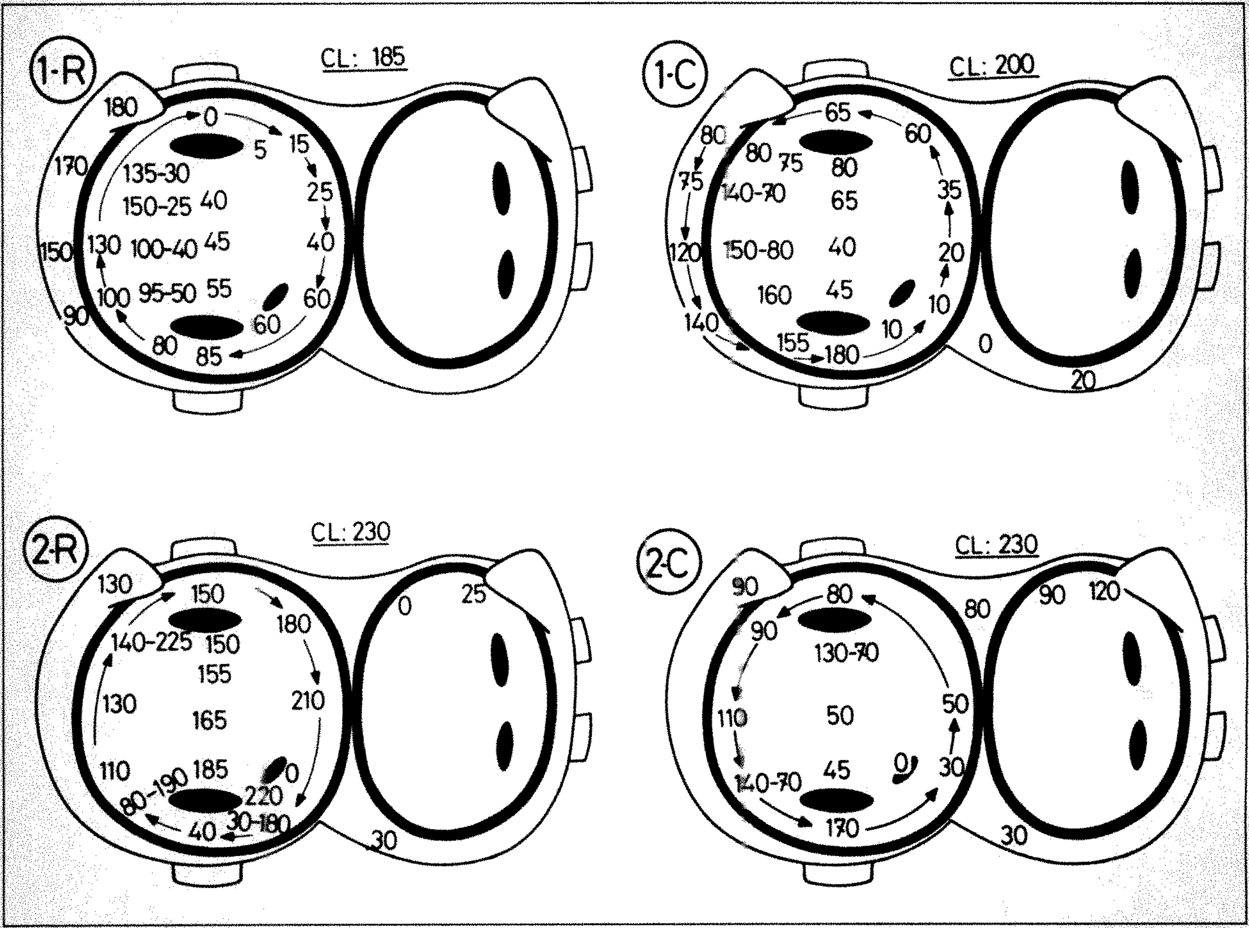

FIGURE 4. Atrial activation maps in cases 1 (*top*) and 2 (*bottom*) during rare (R) and common (C) flutter. The atrial graphic model represents both atria from the mitral and tricuspid rings in a wide-angle view. Atrial appendages and the openings of the superior and inferior venae cavae, coronary sinus and left pulmonary veins are shown. Septal, posterior and lateral right atrial walls are drawn inside the tricuspid ring (endocardial side) and the anterior wall outside (epicardial side). Numbers on the inferior and lateral rim of the mitral ring represent coronary sinus recordings. Double figures indicate the onset of each spike in a double-spike electrogram.

able left atrial activation times coincided roughly with septal activation, but the direction of left atrial activation could not be precisely determined.

Entrainment: During atrial stimulation, entrainment could be demonstrated in cases 1 to 4 and 7 by the presence of progressive fusion and the fixed length of the first postpacing cycle. Cases 3 and 4 also had a change in the electrogram sequence preceding AF interruption. In cases 5 and 6 AF was interrupted during threshold testing, and entrainment was not shown.

DISCUSSION

Rare versus common atrial flutter: These data suggest that most cases of rare AF are due to right atrial macroreentry with clockwise rotation of activation (frontal plane), but that counterclockwise circuits can also produce rare AF patterns. The anatomic pathway seems identical in both types of AF,[1,3,5] and resembles those described by Rosenblueth and García Ramos[6] and Hoffman et al.[7] The ridge separating the inferior vena cava and the tricuspid valve appears as a critical anatomic area closing the activation circle in both,[3,4] but definitive proof of this contention should still be obtained from the effect of limited ablation procedures on this area.

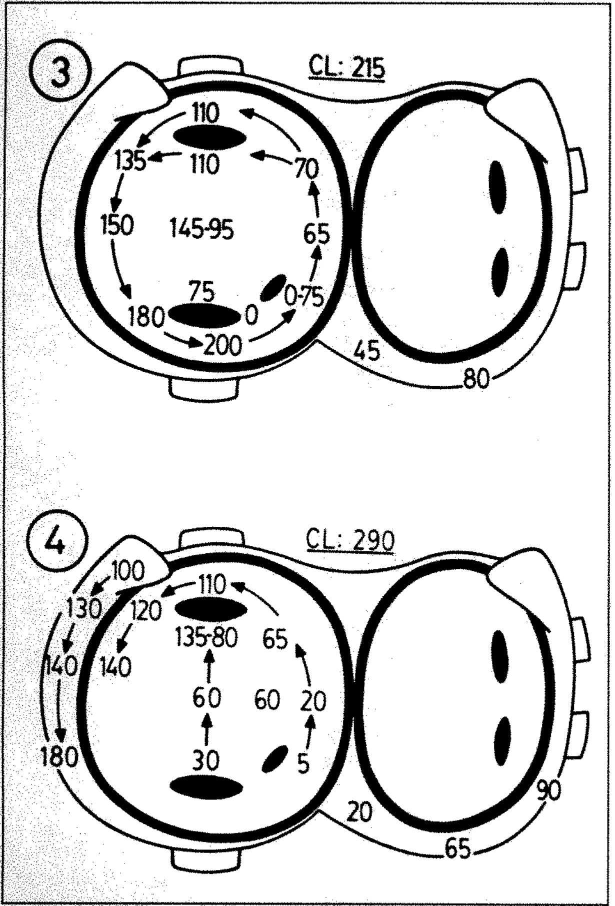

FIGURE 5. Atrial activation maps during rare flutter in cases 3 and 4. For explanation see Figure 4 and text. Note counterclockwise activation of the right atrium.

Puech and Latour[1] reported partial atrial activation mapping in 3 cases of rare AF, suggesting a direction of activation opposite to that in common AF. Beckman et al[5] reported mapping of common and rare AF in the same patient. The maps had >100-ms gaps, but were consistent with right atrial macroreentry in both types of AF, although in opposite directions.

Importance of local conduction block: The separation between activation of the posterior and lateral walls, already described in common AF,[1,3,4] was again a finding in rare AF. Double-spike electrograms recorded between these 2 areas probably reflect local conduction block.[1,3,4] This craniocaudal line of block probably corresponds to the crista terminalis, or posterior internodal pathway, as described by James and Sherf.[8] Slow conduction across the crista terminalis due to anisotropy[9] may thus be an important factor in atrial macroreentry. Fragmented electrograms may be found in other areas, inside or outside the AF circuit, but their significance should be cautiously analyzed in light of the whole activation sequence, because they may represent nonspecific, local and rate-related conduction disturbances.

Limitations: Our data do not clarify the mechanisms underlying the inscription of a positive versus a negative

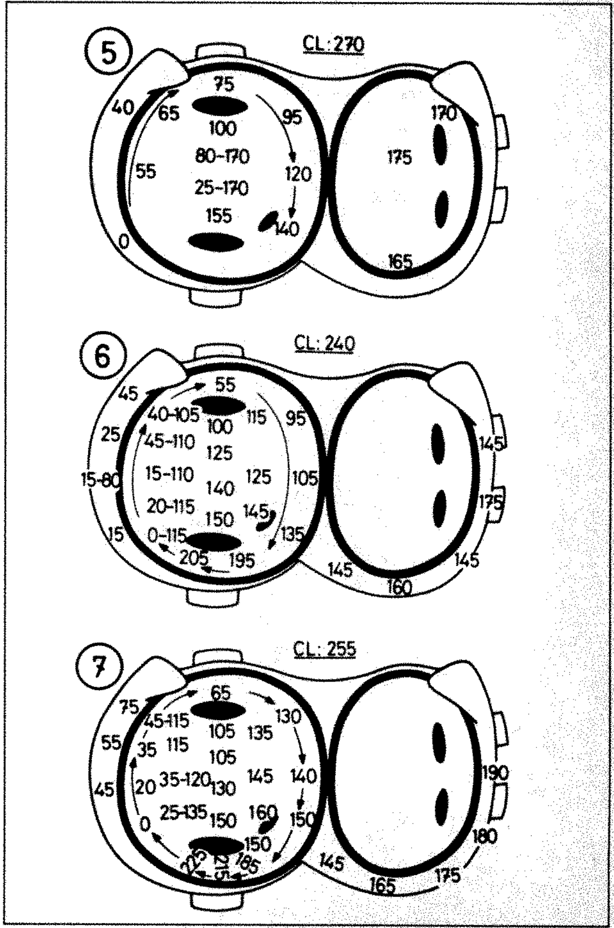

FIGURE 6. Atrial activation maps during rare flutter in cases 5 to 7. For explanation see Figure 4 and text. Note clockwise activation of the right atrium.

deflection. No specific clinical or anatomic background was apparent in our cases of rare AF. The 2 cases with circuits similar to that of common AF suggest that local changes in activation velocity or the synchronization of activation of adjacent, or even distant, portions of atrial myocardium may account for wave morphology,[10] regardless of circuit rotation. Left atrial activation may be important, as suggested by Puech and Latour.[1] We obtained very little information on left atrial activation. In cases 2 and 5 to 7, data from the left atrial endocardium and/or coronary sinus rule out an active role in the circuit, but are not enough to explain wave morphology.

Some of our patients were receiving antiarrhythmic drugs, but clinical observation showed that the addition of the drugs produced changes in AF rate, but not in wave form. The observations in cases 1 and 2, displaying both common and rare AF at different times, also suggest that drug action is not an important determinant of wave morphology.

Two right atrial maps (cases 4 and 5) are incomplete, showing significant gaps in the presumed activation circuit; however, available data strongly support right atrial reentry in both cases.

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Clinical, Echocardiographic and Doppler Correlates of Clinical Instability with Onset of Atrial Fibrillation

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To identify clinical and Doppler echocardiographic correlates of instability with the onset of atrial fibrillation (AF), 87 consecutive patients with new-onset AF who had echocardiograms recorded during that hospital admission while in sinus rhythm were studied. Reviewers who were blinded to echocardiographic and Doppler data classified 51 patients (59%) as unstable because of the development of angina, congestive heart failure, syncope or hypotension with the onset of AF. Echocardiographic and Doppler data on transmitral blood flow velocity were analyzed by a single reviewer who was blinded to other clinical data. Multiple logistic regression analysis identified 3 variables as independent predictors of clinical instability with the onset of AF: (1) history of prior myocardial infarction ($p < 0.02$); (2) echocardiographic evidence of left ventricular dysfunction ($p < 0.03$); and (3) Doppler evidence of increased atrial filling fraction ($p < 0.0001$). An atrial filling fraction threshold of 0.40 had a sensitivity for predicting clinical instability of 80% and a specificity of 72%. These data are consistent with the hypothesis that patients who are more dependent on the atrial contribution to ventricular filling are at increased risk of instability with AF due to the loss of atrial systole.

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The significance of organized atrial contraction was first appreciated by William Harvey in 1628.[1] Several investigators have manipulated atrioventricular synchrony to demonstrate the relative importance of properly timed atrial systole to ventricular performance.[2-4] Left ventricular (LV) performance is also improved after electrical conversion of atrial fibrillation (AF) to normal sinus rhythm.[5,6]

AF is a common clinical problem that is often associated with angina, congestive heart failure, hypotension and syncope. AF is less well tolerated in patients with mitral stenosis, because of fixed mechanical obstruction to mitral inflow, and in patients with systolic ventricular dysfunction due to elevation of end-diastolic volume and pressure.[7,8] Baseline diastolic filling of the left ventricle, independent of the underlying rhythm, may also be impaired in patients with preserved systolic function, particularly in patients with long-standing systemic hypertension.[9,10] Transmitral blood flow velocity can now be evaluated using Doppler echocardiography, a reproducible and inexpensive technique.[11-14] We therefore sought to determine whether the Doppler atrial filling fraction during sinus rhythm was an independent correlate of instability during AF and whether it added information after consideration of routinely available clinical data.

METHODS

Patients: Between January 1, 1985, and December 31, 1988, we identified 498 patients who were admitted to the Brigham and Women's Hospital with a primary discharge diagnosis of AF. From this group, 135 patients were identified (1) with presumed new-onset AF (documented in the hospital or with presenting symptoms <48 hours in duration), and (2) who had an echocardiogram during the index admission. Three patients with known mitral stenosis were excluded because of the resulting disturbance in resting transmitral flow. Forty-two patients were excluded from the study because an echocardiogram was recorded only while the patient had AF. Three patients were excluded because the echocardiogram was technically inadequate. Thus, of the initial 135 patients, 87 had technically adequate echocardiograms while in sinus rhythm. Of the 87 patients in the study group, 27 (31%) developed AF while in the hospital.

Clinical parameters were recorded from medical records by 2 reviewers blinded to echocardiographic and

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TABLE I Baseline Clinical Characteristics

	Stable (n = 36)	Unstable (n = 51)	p Value
Age (years)	61 ± 12	66 ± 13	NS
Men/women	19/17	24/27	NS
History of			
AF	16 (44%)	16 (31%)	NS
CHF	8 (22%)	11 (21%)	NS
SH	16 (44%)	18 (35%)	NS
Angina	8 (22%)	19 (37%)	NS
MI	2 (5%)	11 (21%)	<0.05
COPD	2 (5%)	4 (7%)	NS
MR	3 (8%)	4 (7%)	NS
AS	0 (0%)	9 (17%)	<0.01
AR	2 (5%)	2 (3%)	NS

AF = atrial fibrillation; AR = aortic regurgitation; AS = aortic stenosis; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; MR = mitral regurgitation; NS = not significant; SH = systemic hypertension.

TABLE II Data at Presentation

	Stable (n = 36)	Unstable (n = 51)
Palpitations	6 (16%)	17 (33%)
Angina pectoris	0	29 (56%)
CHF	0	32 (62%)
Hypotension	0	9 (18%)
Syncope	0	6 (12%)
Heart rate (beats/min)	111 ± 34	108 ± 30
Systolic BP (mm Hg)	124 ± 25	127 ± 30
Diastolic BP (mm Hg)	72 ± 13	71 ± 23
Peripheral edema	3 (8%)	14 (28%)
Rales	0	11 (22%)

BP = blood pressure; CHF = congestive heart failure.

Doppler data. These included age, gender, symptoms at time of presentation, medical history including prior history of AF, angina, myocardial infarction, congestive heart failure, hypertension, chronic obstructive pulmonary disease, mitral regurgitation, aortic stenosis or aortic regurgitation, physical examination at the time of presentation, hospital course and long-term follow-up when available.

Fifty-two patients took medications on a long-term basis, including 29 taking digoxin, 14 taking β blockers and 9 calcium channel blockers. Sixty patients required chemical cardioversion including 16 with digoxin alone, 26 with quinidine sulfate, 10 with procainamide and 8 with other agents. Of the remaining patients, 14 underwent spontaneous cardioversion and 13 required electrical cardioversion, 9 of these after unsuccessful drug trials.

Patients were classified as "unstable" if they developed any of the following events with AF: hypotension (systolic blood pressure <90 mm Hg); angina (chest pain judged by ≥ 2 independent physicians to be consistent with ischemia or chest pain with an ST-segment depression ≥ 1 mm in ≥ 2 leads); congestive heart failure documented by both physical examination and radiography; and syncope defined as witnessed loss of consciousness.

Doppler echocardiograms: Doppler echocardiograms were obtained after (mean 2.1 ± 1.6 days) reversion to sinus rhythm in 73 patients. Fourteen patients had echocardiograms recorded before (mean 4.6 ± 3.0 days) onset of AF. Pulsed-wave Doppler sampling of transmitral flow was recorded from the apical 4-chamber view with the sample volume located below the mitral valve anulus and above the leaflet tips (parallel to the direction of flow) using a Hewlett-Packard 77020 AC/AR phased-array ultrasonoscope device using a 2.5-MHz transducer. Transmitral Doppler flow velocity profiles were digitized and analyzed using a Cardiology Workstation (GTI Freeland Medical Division). A minimum of 3 spectral envelopes were analyzed and averaged for each measurement. Modal peak velocities ("E velocity" and "A velocity") and velocity time integrals were calculated. The early diastolic velocity time integral (VTI E) and late diastolic time integral (VTI A) were calculated. When these areas overlapped, VTI A was defined as the portion of the diastolic velocity time integral over that expected if the slope of deceleration of the VTI E continued to baseline, as previously described.[15]

LV function was assessed by 2-dimensional echocardiograms obtained from the parasternal short-axis, parasternal long-axis, apical 2-chamber and apical 4-chamber views. Systolic ventricular function was scored as normal, mildly reduced, moderately reduced or severely reduced as recorded by the initial staff review of the echocardiogram. The presence of LV hypertrophy was assessed from the 2-dimensional echocardiogram and from the M-mode examination using American Society for Echocardiography standards.[16] The presence of valvular regurgitation or stenosis was obtained from the printed echocardiographic report accompanying each study. Aortic stenosis was defined as a peak instantaneous gradient of >16 mm Hg.

Statistical analysis: In the univariate analysis, associations between clinical instability and possible predictors were examined using the chi-square test with appropriate degrees of freedom for categoric variables and the Student's *t* test for continuous variables after testing to see that these variables had a normal distribution. Variables from the medical history that were evaluated included age, gender, and histories of AF, congestive heart failure, angina, myocardial infarction, hypertension, chronic obstructive pulmonary disease, mitral regurgitation, aortic stenosis and aortic regurgitation. Variables from the echocardiographic evaluation included the presence of LV hypertrophy, LV function, evidence of mitral regurgitation, evidence of aortic stenosis, evidence of aortic regurgitation and left atrial enlargement. The Doppler echocardiographic variables included E velocity, A velocity, ratio of E velocity to A velocity, VTI E, VTI A, the ratio of VTI E to VTI A (VTI E/VTI A), and the atrial filling fraction as defined by VTI A/(VTI E + VTI A). A multiple logistic regression analysis was then performed in which all clinical factors and atrial filling fraction, the Doppler parameter of interest, were included. In the primary multivariate analysis, patients with aortic stenosis were excluded since all 9 of these patients were clinically unstable. In a secondary analysis that included the patients with aortic stenosis, the coefficients for the other potential predictors were nearly identical. Therefore, only the primary analysis is presented. Finally, the diagnostic performance in terms of sensitivity and specificity of serial values of atrial filling fraction was used to generate a receiver-operating characteristic curve.

RESULTS

Patient characteristics: Of 87 patients, 51 (59%) were unstable with new-onset AF (Table I). Of these patients, 29 (57%) developed angina, 32 (63%) developed congestive heart failure, 6 (12%) had syncopal episodes and 9 (18%) developed hypotension (systolic blood pressure <90 mm Hg) (Table II).

Historical characteristics: Of the 11 clinical variables included in the univariate analysis (Table I), only a history of prior myocardial infarction ($p < 0.05$) or of aortic stenosis ($p < 0.01$) had statistically significant associations with clinical outcome.

Doppler echocardiography: The degree of LV dysfunction on the 2-dimensional echocardiogram was significantly associated with unstable presentation, but the presence of LV hypertrophy and left atrial enlargement were not (Table III). Nine patients in the unstable group had aortic stenosis compared with none in the stable group; all 9 patients with Doppler evidence of aortic stenosis had a history of aortic stenosis as well.

All Doppler parameters of atrial contribution to the transmitral flow profile had statistically significant associations with unstable presentations. By univariate analysis, the atrial filling fraction, the primary Doppler parameter of interest, was very highly associated with unstable presentation ($p < 0.0001$). E velocity and VTI E did not correlate with outcome.

Multivariate analysis: Logistic regression controlling for all clinical and echocardiographic variables identified atrial filling fraction as the single most powerful predictor of clinical instability ($p < 0.0001$). A history of myocardial infarction ($p < 0.02$) and LV dysfunction ($p < 0.03$) were the only other variables of statistical significance in the multivariate analysis. Increased age was not an independent predictor of instability.

Receiver-operating characteristic curve: The diagnostic performance of atrial filling fraction at various thresholds was used to generate a receiver-operating characteristic curve (Figure 1). Using a cutoff atrial filling fraction of 0.40, the sensitivity for predicting instability was 80%, the specificity was 72% and the relative risk was 2.7. This cutoff value generated the highest chi-square value (22.53), suggesting that it is best able to discriminate stable from unstable patients.

DISCUSSION

The goal of the study was to identify clinical and echocardiographic features that might predict an adverse clinical response to the development of AF. The prior hypothesis was that patients with greater atrial filling fractions would tolerate the loss of atrial systole poorly compared to patients with smaller atrial filling fractions. Univariate analysis of the patient clinical characteristics revealed history of prior myocardial infarction or aortic stenosis to be the only statistically significant non–Doppler clinical predictor of adverse outcome. The 2-sample *t* test for age approached but did not achieve statistical significance, an important point given the known influence of normal aging on Doppler-derived indexes of LV filling.[17-20] With regard to the 2-dimensional echocardiographic features analyzed, only overall LV function had a statistically significant association with clinical outcome. Aortic stenosis was present in 9 patients in each case by both history and echocardiographic examination; all were in the unstable group.

TABLE III Echocardiography Data in Sinus Rhythm

	Stable	Unstable	p Value
LV hypertrophy	15 (41%)	28 (55%)	NS
LV dysfunction	7 (19%)	17 (33%)	<0.05
Mitral regurgitation	6 (17%)	8 (16%)	NS
Aortic regurgitation	4 (11%)	7 (14%)	NS
Aortic stenosis	0	9 (18%)	<0.01
Left atrial enlargement	17 (47%)	19 (37%)	NS
Doppler			
E velocity	68 ± 16	61 ± 18	NS
A velocity	58 ± 19	72 ± 16	<0.0006
E veloc/A veloc	1.25 ± 0.38	0.85 ± 0.20	<0.0001
VTI E	10.4 ± 3.8	9.7 ± 3.8	NS
VTI A	6.0 ± 2.0	8.4 ± 2.3	<0.0001
VTI E/VTI A	1.7 ± 0.5	1.2 ± 0.5	<0.0001
AFF	0.37 ± 0.06	0.48 ± 0.09	<0.0001

AFF = atrial filling fraction; LV = left ventricle; NS = not significant; VELOC = velocity; VTI = velocity time integral.

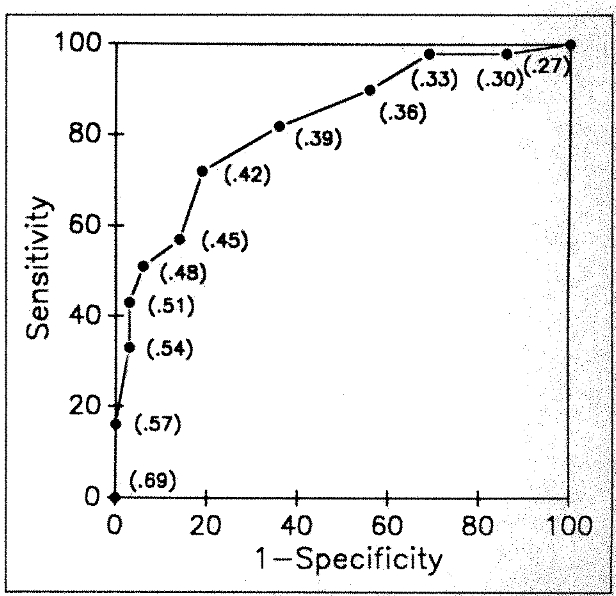

FIGURE 1. Receiver-operating characteristics curve for Doppler atrial filling fraction for the discrimination of stable versus unstable presentation. Numbers in parentheses correspond to Doppler atrial filling fractions.

Multivariate analysis of a variety of clinical and echocardiographic variables revealed atrial filling fraction to be the single most powerful predictor of clinical outcome followed by history of prior myocardial infarction and echocardiographic evidence of LV dysfunction.

This study design has several potential limitations. Patients were selected with either documented or presumed new-onset AF. Whereas most cases had absolute documentation as to the onset of AF, there were several cases in which onset was dated by change in subjective symptoms. In these cases, only patients whose subjective change had persisted for ≤48 hours were included. Manning et al[21] observed that the atrial contribution to LV filling was abnormal immediately after cardioversion in patients with chronic AF. By including only patients with new-onset AF, confounding by potential loss of atrial mechanical activity by chronic AF was minimized. Because most echocardiograms were recorded after conversion to sinus rhythm, the possibility that an unstable clinical status somehow causes a subsequent increase in atrial filling fraction cannot be excluded.

Because an increased atrial filling fraction is related to abnormal LV relaxation,[22] it is attractive to hypothesize that patients with impaired relaxation are likely to tolerate AF poorly. However, multiple factors such as preload and afterload affect the Doppler transmitral flow profile.[22,23] Choong et al,[24] for example, demonstrated marked alterations in early filling as assessed by alterations in various transmitral Doppler indexes in response to nitroglycerin infusion; these results have been confirmed with radionuclide ventriculography.[25] Thus, although it is not possible to identify the precise factors causing the increased atrial filling fraction in our unstable patients, the conclusion that an increased atrial filling fraction is important in the clinical response to new-onset AF is still supported.

These data support the hypothesis that the atrial filling fraction is closely correlated with the hemodynamic response to new-onset AF. The multivariate analysis confirmed that, even after adjusting for other clinical data, patients with prior myocardial infarction, LV dysfunction or increased atrial filling fraction are less likely to tolerate new AF without important clinical sequelae.

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Day-to-Day Reproducibility of Antiarrhythmic Drug Trials Using Programmed Extrastimulus Techniques for Ventricular Tachyarrhythmias Associated with Coronary Artery Disease

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Forty-nine patients with coronary artery disease and documented clinical sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) were studied twice in the drug-free state and twice during treatment with an identical antiarrhythmic medication at therapeutic plasma concentrations using an identical programmed electrical stimulation protocol. Tested drugs included procainamide, quinidine, disopyramide and phenytoin. During their 2 paired tests, 11 patients had nearly identical therapeutic plasma concentrations of antiarrhythmic agents (group I) and 38 patients had therapeutic plasma concentrations, but with more variation in drug levels between otherwise identical paired drug tests (group II). Overall, 71% of patients had inducible sustained VT or VF during drug testing. Induced ventricular arrhythmias were not reproducible in 45% of group I patients, despite restudy at nearly identical therapeutic plasma concentrations of an identical antiarrhythmic agent. Induced arrhythmias were also not reproducible in 16% of group II patients. This variability could not be attributed to the electrophysiologic characteristics of the patients studied. Drug trials directed by programmed stimulation should be cautiously interpreted because time-associated changes can mimic a change attributed to a beneficial or deleterious drug effect.

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Previous studies have shown that there is significant day-to-day variability in ventricular tachyarrhythmias induced during programmed intracardiac electrophysiologic stimulation in the absence of any therapeutic intervention.[1,2,3] How the addition of antiarrhythmic therapy may influence such variability is not known. This study was undertaken to determine the day-to-day reproducibility of acute antiarrhythmic drug trials directed by programmed stimulation.

METHODS

Population: We evaluated 150 consecutive patients (128 men and 22 women, 61.7 ± 10.3 years of age) with documented sustained clinical ventricular tachycardia (VT) (72 patients) or ventricular fibrillation (VF, 78 patients) not associated with an acute myocardial infarction. All patients underwent 2 paired programmed intracardiac electrophysiologic tests in the drug-free state. This study focused on 49 of these patients (43 men, 6 women, mean age 61.6 ± 9.5 years) who had coronary artery disease and clinical VT (24 patients) or VF (25 patients) and who underwent 2 paired electrophysiologic studies during treatment with an identical antiarrhythmic medication at therapeutic plasma concentrations. These patients were studied twice in the drug-free state and twice while treated with the same antiarrhythmic medication as part of an ongoing evaluation of the reproducibility of electrophysiologic testing, as well as for clinical indications (to assess pharmacologic control of their rhythm disturbances). The selection of patients and drugs for restudy rested upon patients' willingness to be retested during treatment with a clinically tolerated antiarrhythmic medication at therapeutic concentrations. No patients were retested based upon their electrophysiologic response in the drug-free state, nor upon the nature of their clinical arrhythmia. None had experienced a myocardial infarction within 6 weeks of electrophysiologic study.

Stimulation protocol: Informed consent and prior approval of the Human Subjects Review Committee of the Oregon Health Sciences University were obtained. All patients underwent 2 baseline electrophysiologic studies, 6 to 24 hours apart in the absence of antiarrhythmic agents. Our stimulation protocol has been previously reported and included rapid pacing (6 beats at 400 ms and 600 ms fixed cycle lengths, synchronized to

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TABLE I Loading and Maintenance Dosing Regimen for Antiarrhythmic Agents Used During Electrophysiologic Evaluation

Medication	Loading Dose	Maintenance Dose	Therapeutic Range (μg/ml)
Procainamide	15 mg/kg IV	0.80 to 0.1 mg/kg/min	4 to 20
Quinidine gluconate	15 mg/kg IV	0.02 to 0.04 mg/kg/min	2 to 6
Disopyramide	15 mg/kg po*	300 mg po every 6 hrs	2 to 6
Phenytoin	20 mg/kg po*	300 mg po every day	10 to 20

* Given in 4 to 5 divided doses over 24 hours.

the previous spontaneous R wave) followed by programmed pacing from the right ventricle using up to 4 extrastimuli (at 5 mA and 2 ms pulse duration).[3] Stimulation thresholds were measured before each study, averaged 0.7 mA, and only rarely exceeded 1 mA. Stimulation was terminated upon induction of a sustained ventricular tachyarrhythmia or upon completion of the entire stimulation protocol thru 4 ventricular extrastimuli. Stimulation during serial drug testing followed an identical protocol.

Drug testing: After 2 drug-free studies, all patients were serially tested with procainamide, quinidine, disopyramide and phenytoin unless a history of drug allergy, medication intolerance or the severity of left ventricular dysfunction made a particular choice imprudent. The ability to test patients a second time during treatment with an identical drug and the selection of the medications to be retested were dependent upon these concerns. Patients who were free of inducible arrhythmias while drug free and who were likely to require antiarrhythmic medications for other indications (supraventricular arrhythmias) were tested with drugs in order to exclude any possibility of proarrhythmia. To promote the presence of steady-state plasma drug concentrations at the time of testing, patients received either an intravenous or oral loading dose of an antiarrhythmic medication, followed by a maintenance dosing schedule for 6 to 36 hours before programmed stimulation (Table I). Sequential electrophysiologic tests of an identical antiarrhythmic drug were performed within 6 to 48 hours of one another during such a maintenance dosing schedule. Plasma levels of antiarrhythmic agents at the time of programmed stimulation were obtained immediately after completion of each test.

Definitions: RHYTHMS: REPETITIVE VENTRICULAR RESPONSE: 1 to 3 ventricular beats after capture of the last ventricular pacing stimulus.

NONSUSTAINED VENTRICULAR TACHYCARDIA: ≥4 ventricular beats (lasting ≤30 seconds) after capture of the last pacing stimulus, not requiring therapeutic intervention.

SUSTAINED VENTRICULAR TACHYCARDIA: VT lasting >30 seconds or requiring intervention.

VENTRICULAR FIBRILLATION: completely disorganized surface cardiac electrical activity necessitating therapeutic intervention.

TABLE II Rhythm and Diagnoses in Patients Undergoing 2 Electrophysiologic Tests During Treatment with Identical Antiarrhythmic Agents

Patient Characteristics	Group I n = 11	Group II n = 38	p Value
Clinical rhythm diagnosis			
Ventricular fibrillation	6 (55%)	19 (50%)	0.9
Ventricular tachycardia	5 (45%)	19 (50%)	0.9
Drug-free programmed stimulation results			
Inducible sustained VT/VF	9 (82%)	35 (92%)	0.7
Reproducible arrhythmias	7 (64%)	29 (76%)	0.6
Antiarrhythmic drug trials			
Procainamide	2 (18%)	26 (68%)	0.004
Quinidine	5 (45%)	5 (13%)	0.03
Disopyramide	1 (9%)	3 (8%)	0.9
Phenytoin	3 (27%)	4 (11%)	0.2

NONREPRODUCIBLE ARRHYTHMIAS: provocation of sustained VT or VF during one electrophysiologic study, with a failure to induce a sustained VT or VF during the comparison study.

Therapeutic total plasma concentrations were defined for each tested antiarrhythmic medication based upon conventional criteria.[4,5]

Two electrophysiologic tests were defined as comparable only if all of the following 5 criteria were met: both tests were performed during treatment with an identical antiarrhythmic medication; no change in antiarrhythmic medication dosage transpired between studies; no new clinical events (such as myocardial infarction or cardiac surgery) or changes in other medications (digitalis, β blockers, calcium antagonists, diuretics or afterload reducing medications) transpired between the performance of successive electrophysiologic studies; the plasma concentration was within the therapeutic range for the antiarrhythmic agent; and this value varied by ≤10% of the minimum acceptable therapeutic plasma concentration for the drug between each study. For quinidine and disopyramide, for example, a minimum plasma concentration of 2 μg/ml, which varied by ≤0.2 μg/ml between studies, was required; for procainamide a minimum concentration of 4 μg/ml that varied by ≤0.4 μg/ml and for phenytoin, a minimum plasma concentration of 10 μg/ml that varied by ≤1 μg/ml between studies was required.

Two electrophysiologic tests were of limited comparability if therapeutic plasma concentrations varied by >10% or a change in medication dose transpired between otherwise identical studies.

These criteria—for inducibility, reproducibility and acceptable plasma concentrations of antiarrhythmic agents—were all defined before data review and analysis.

Statistical analysis: Statistical analysis was performed using a 2-tailed chi-square or Fisher's exact test. A p value <0.05 was defined as significant.

RESULTS

Patients: The 49 patients underwent a total of 240 separate electrophysiologic tests, including 49 paired drug-free tests and 71 paired tests during treatment with an identical antiarrhythmic drug (31 paired tests during treatment with procainamide, 17 during quinidine treatment, 7 during disopyramide treatment and 16 paired electrophysiologic tests during treatment with phenytoin). If patients were serially tested with >1 antiarrhythmic drug, only the response to the first tested drug was reported.

Of the 49 patients who were tested twice during treatment with an identical antiarrhythmic medication at therapeutic plasma concentrations, 11 (22%) met criteria for having comparable electrophysiologic tests during drug therapy (group I). Thirty-eight patients had electrophysiologic studies that were of limited comparability because of either wider than allowable differences in therapeutic plasma concentrations between studies or had doses of these antiarrhythmic medications altered between successive tests (group II). Both groups underwent an identical stimulation protocol.

The clinical rhythm disturbance (VT versus VF) and drug-free electrophysiologic characteristics of the 11 patients who made up group I were similar to those of the 38 group II patients (Table II). During drug evaluation, proportionately fewer patients were tested twice during treatment with procainamide and more during treatment with quinidine in group I than in group II; use of phenytoin and disopyramide did not significantly differ between groups (Table II).

Induction of sustained ventricular arrhythmias during drug testing: Nine of the 11 patients in group I (82%) had inducible sustained VT or VF during at least 1 of their 2 drug-free electrophysiologic studies. Two patients without previously induced sustained ventricular tachyarrhythmias during baseline testing, in addition to 6 patients with inducible sustained VT or VF during baseline testing, had inducible sustained arrhythmias during drug testing directed by programmed stimulation. That is, a total of 8 of 11 group I patients (73%) repeatedly studied with the same antiarrhythmic agent developed sustained VT or VF in response to programmed extrastimuli during at least 1 of their 2 identical drug studies. Of these 8 patients, 2 (25%) had an inducible sustained ventricular arrhythmia after rapid right ventricular pacing, 2 patients after addition of a single ventricular extrastimulus, 1 patient (13%) after 3 extrastimuli and 3 patients (37%) after 4 ventricular extrastimuli (Figure 1).

Similar findings were observed in group II (difference not significant compared to group I): Thirty-five of the 38 patients in group II (92%) had inducible sustained VT or VF during at least 1 of their 2 drug-free electrophysiologic studies. Twenty-seven of these 35 patients with inducible sustained VT or VF during baseline testing had inducible sustained arrhythmias during drug testing directed by programmed stimulation. No patient without inducible VT or VF during drug-free programmed stimulation developed a sustained ventricular arrhythmia during drug testing. Thus, a total of 27 of 38 (71%) patients studied twice with the same antiarrhythmic agent developed sustained VT or VF in response to programmed extrastimuli during at least 1 of their 2 identical drug studies. Of these 27 patients, 3 (11%) had an inducible sustained ventricular arrhythmia after rapid right ventricular pacing, 7 patients

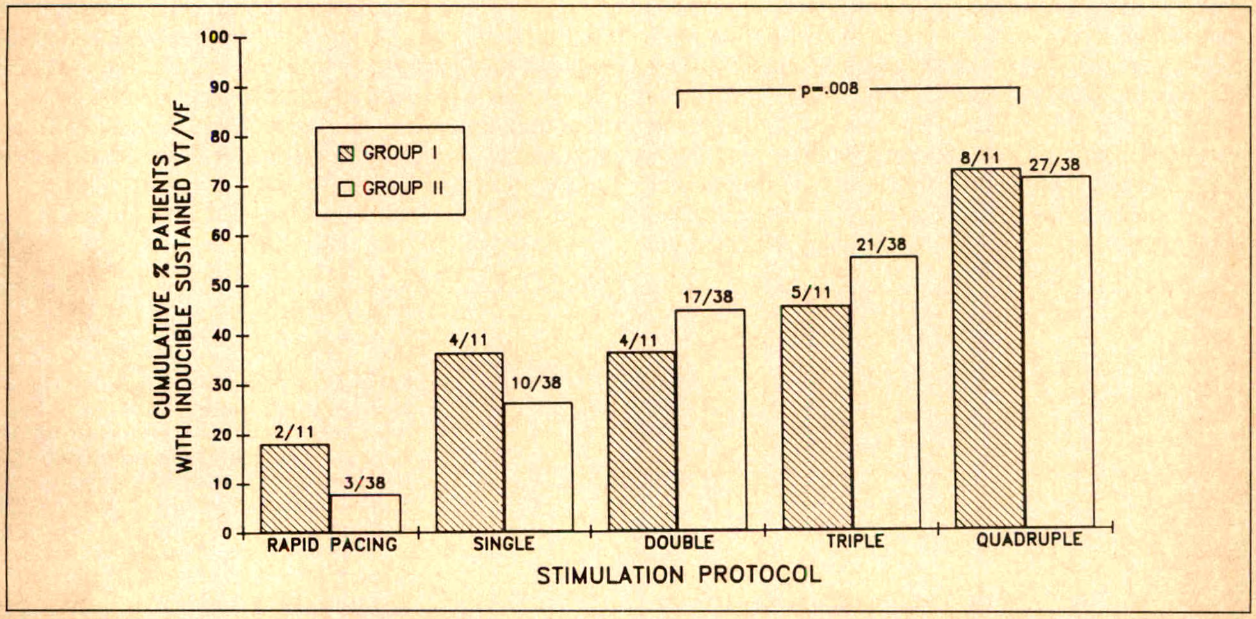

FIGURE 1. The inducibility of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with (group I) and without (group II) completely comparable electrophysiologic tests, during treatment with antiarrhythmic medications. The numerator of each fraction represents the cumulative number of patients in whom a sustained ventricular tachyarrhythmia was induced by that point in the stimulation protocol. The denominator represents the total number of patients in groups tested. Subjects, for example, who had reached an end point with rapid pacing, single, double or triple protocols contributed to quadruple stimulation protocol results. The p value depicts differences between double and quadruple protocols, when groups I and II are combined. Components of the stimulation protocol are as follows: single = single programmed extrastimulus; double = up to 2 programmed extrastimuli; triple = up to 3 programmed extrastimuli; quadruple = up to 4 programmed extrastimuli.

TABLE III Plasma Concentrations of Antiarrhythmic Agents, Differences in such Concentrations Between Paired Electrophysiologic Tests

	Plasma Concentration (μg/ml)	
Medication Tested	Group I	Group II
Procainamide	(n = 2)	(n = 26)
Test no. 1	13.0 ± 1.1	11.9 ± 4.5
Test no. 2	12.7 ± 1.0	12 ± 7
Difference*	0.3 ± 0.1	7.8 ± 4.9
Quinidine	(n = 5)	(n = 5)
Test no. 1	3.9 ± 0.4	3.9 ± 1
Test no. 2	3.9 ± 0.5	3.1 ± 0.6
Difference*	0.08 ± 0.08	1.1 ± 0.6
Disopyramide	(n = 1)	(n = 3)
Test no. 1	3.6	4.9 ± 0.9
Test no. 2	3.6	2.8 ± 1.2
Difference*	0	2.2 ± 1.3
Phenytoin	(n = 3)	(n = 4)
Test no. 1	14 ± 2	14 ± 3
Test no. 2	14 ± 1.3	11.2 ± 4
Difference*	0.3 ± 0.6	4.4 ± 2.4

* Difference in paired antiarrhythmic plasma concentrations achieved during the first and second electrophysiologic tests (test no. 1 versus test no. 2).

(26%) after the addition of a single ventricular extrastimulus, 7 patients (26%) after 2 extrastimuli, 4 patients (15%) after 3 extrastimuli and 6 patients (22%) after 4 ventricular extrastimuli (Figure 1). Plasma concentrations of antiarrhythmic medications tested in group I and II are listed in Table III.

Reproducibility: Induced ventricular arrhythmias were not reproducible in 5 of 11 group I patients (45%), despite restudy at nearly identical therapeutic plasma concentrations of an identical antiarrhythmic agent at an identical dose, using an identical stimulation protocol. By comparison, 6 of 38 group II patients (16%) manifested nonreproducible ventricular arrhythmias between paired identical-drug tests, at wider allowable therapeutic plasma concentrations or drug dosing schedules (p >0.16, Figure 2). This day-to-day variability in arrhythmias induced during drug testing was comparable to the day-to-day variability observed during serial testing in the drug-free state in both group I (45 versus 36%, respectively, p >0.9) and group II (16 vs 24%, respectively, p >0.8). The occurrence of such variability during drug testing could not be predicted by the response from drug-free programmed stimulation. All 5 patients with nonreproducible arrhythmias during drug testing in group I, and 5 of the 6 patients with nonreproducible arrhythmias in group II, for example, had reproducibly induced arrhythmias during paired drug-free programmed stimulation.

In the combined group of 49 patients, both inducible as well as nonreproducible arrhythmias were observed more frequently with a testing protocol employing up to 4 extrastimuli compared to only 2 extrastimuli (p = 0.008 and p = 0.04, respectively, Figures 1, 2). Inducibility and nonreproducibility did not significantly differ between protocols using 2 versus 3 (p >0.4 and p >0.7, respectively) or 3 versus 4 (p = 0.1, respectively) extrastimuli. In this combined group of 49 patients, reproducibility did not vary significantly whether the clinical rhythm diagnosis was VT or VF (p >0.9, Table IV).

As had been previously observed in the drug-free state, the day-to-day variability in rhythms induced during repeated drug studies appeared to be random. That is, rhythms were just as likely to "worsen" (become sustained; 5 of 11 patients) as they were to improve (become nonsustained or noninducible; 6 of 11 patients) when identical drug tests were repeated (p >0.9, Table IV).

DISCUSSION

Clinically important changes in the characteristics of an induced ventricular arrhythmia have been reported in up to 27% of patients with clinical sustained ventricular arrhythmias, who undergo repeated electrophysiologic testing in the absence of any therapeutic intervention.[3] This study extends these observations to antiarrhythmic drug trials directed by programmed electrical stimulation, which used an identical stimulation protocol.

A total of 11 of 49 patients (22%) had significant day-to-day variability in results of electrophysiologic

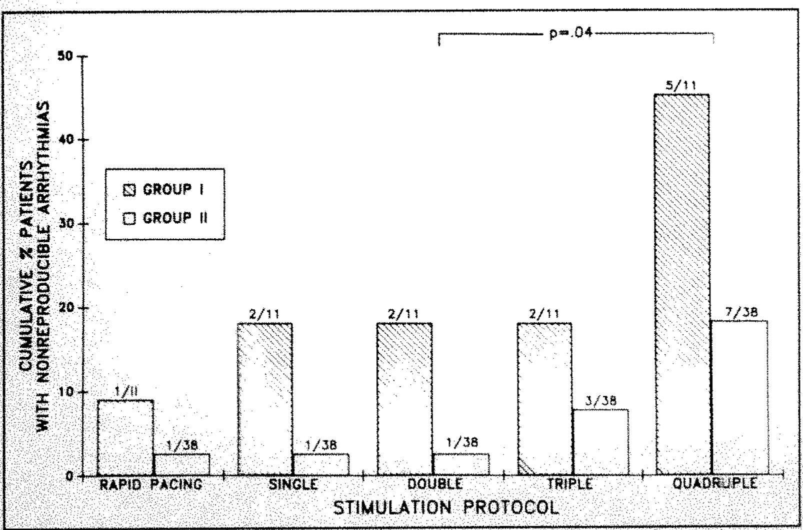

FIGURE 2. The nonreproducibility of induced ventricular arrhythmias (defined as provocation of sustained ventricular tachycardia or ventricular fibrillation during 1 electrophysiologic study with a failure to induce a sustained ventricular tachyarrhythmia during the comparison study) among patients with (group I) and without (group II) completely comparable paired PES tests during treatment with an identical antiarrhythmic medication. The p value depicts differences between double and quadruple protocols, when groups I and II are combined. Definition of fractions and components of the stimulation protocol are as defined in Figure 1.

testing while under cover of even nearly identical therapeutic concentrations of identical antiarrhythmic medications. While the magnitude of this variability was similar to that observed during drug-free electrophysiologic tests in these patients, its occurrence was not limited solely to patients manifesting nonreproducible arrhythmias during predrug testing. Such variability was also as common in patients with a clinical history of sustained VT as it was in those with VF.

Previous studies of reproducibility: No previous study has specifically addressed the day-to-day reproducibility of antiarrhythmic drug trial results using such stringent criteria for comparability. The short-term reproducibility for suppression of inducible sustained VT or VF by drug therapy has been reported by Ruskin and Garan to range from 94 to 97%.[6,7,8] The latter figures may, however, overestimate the degree of reproducibility that is actually present during drug testing. In such investigations, only patients whose arrhythmias were rendered noninducible by an antiarrhythmic agent during their first electrophysiologic test were customarily restudied. The corresponding group of patients (who had inducible arrhythmias during drug testing) has not, to our knowledge, been similarly evaluated. Our data, based upon retesting of all patients regardless of what arrhythmias were induced at first study, identified more variability in programmed stimulation than previously reported. We found this variability to be bidirectional; upon restudy, rhythms were as likely to become sustained as they were to become nonsustained or noninducible (Table IV).

TABLE IV Clinical Characteristics and Results of Programmed Stimulation in Patients with Nonreproducible Arrhythmias During Paired Testing of Identical Antiarrhythmic Agents

				Results	
Group	Sex	Clinical Rhythm	Drug Tested	Test No. 1	Test No. 2
I	M	VT	Pa	VT (200 beats/min)	RVR (1 beat)
	M	VT	Qu	RVR (1 beat)	VT (175 beats/min)
	M	VF	Qu	NSVT (20 beats at 280 beats/min)	VT (280 beats/min)
	M	VF	Ph	VF	RVR (2 beats)
	M	VF	Ph	RVR (2 beats)	VF
II	M	VF	Pa	VT (210 beats/min)	RVR (3 beats)
	M	VF	Pa	VT (150 beats/min)	RVR (2 beats)
	M	VT	Pa	VT (215 beats/min)	NSVT (25 beats at 180 beats/min)
	M	VF	Qu	VF	NSVT (18 beats at 270 beats/min)
	M	VF	Di	NSVT (9 beats at 180 beats/min)	VT (250 beats/min)
	M	VT	Ph	NSVT (11 beats at 220 beats/min)	VT (215 beats/min)

Di = disopyramide; NSVT = nonsustained ventricular tachycardia; Pa = procainamide; Ph = phenytoin; Qu = quinidine; RVR = repetitive ventricular response; VF = sustained ventricular fibrillation; VT = sustained ventricular tachycardia.

A number of factors may account for the variability seen in arrhythmias during testing with identical drugs at similar plasma concentrations, such as variations in patient autonomic tone, stimulation protocol, and changes in stimulation threshold (we observed no significant differences in threshold among patients who had nonreproducible arrhythmias).[3,9,10] However, other factors may be unique to antiarrhythmic drug trials directed by programmed stimulation. For example, the presence and quantities of active drug metabolites might influence such test results. Day-to-day differences in plasma protein binding (not assessed by this study) could alter the amount of "free" (unbound) drug available to produce an antiarrhythmic effect. Furthermore, acute plasma drug concentrations may not necessarily correspond to myocardial tissue levels. Particularly when patients are exposed to plasma levels of antiarrhythmic agents for longer periods of time, a greater degree of tissue penetration may occur, which may alter the arrhythmia substrate to a greater degree than reflected by plasma concentrations.

However, if drug metabolites or duration of therapy exert an influence upon the variability observed in results of programmed stimulation, this effect is not readily predictable. Marchlinski et al[11] reported a 100% concordance in results of programmed stimulation between intravenous and oral procainamide at similar therapeutic plasma concentrations, despite a major difference in N-acetylprocainamide (NAPA) concentrations and 2 to 5 days of ongoing procainamide therapy between the 2 studies. Others have suggested that N-acetylprocainamide is considerably less potent than procainamide, and probably does not significantly contribute to the effects of its parent drug.[12-14]

We observed an important degree of discordance in results of programmed electrical stimulation not only when patients were acutely restudied during continued treatment with intravenous procainamide but also during repeated testing of other antiarrhythmic drugs at approximately equal therapeutic plasma concentrations. Phenytoin is not known to have metabolites with active electrophysiologic properties; metabolites of quinidine and disopyramide are infrequently found in such concentrations or potency to rival the antiarrhythmic properties of the parent drug.[15] Yet, patients treated with these medications manifested a degree of day-to-day variability comparable to that observed during treatment with procainamide.

Limitations: The selection of patients and drugs for restudy was not prospectively determined, but depended upon patients' clinical tolerance of tested drugs at therapeutic concentrations, and their willingness to be retested. The gender, age and electrophysiologic characteristics of the study patients did not differ from those who were not studied twice during drug treatment. Moreover, criteria for inducibility, reproducibility and acceptable plasma concentrations of antiarrhythmic agents were determined prospectively, before data review.

Newer pharmacologic agents were not evaluated by this study. It is not clear whether day-to-day variability in the results of programmed stimulation is limited to only certain classes of antiarrhythmic drugs.

This study did not include an analysis of rhythm morphology as a criterion for reproducibility. The clinical relevance of rhythm configuration during drug testing is controversial. Even among patients with clinical sustained VT of a single morphology, most may manifest multiple morphologically distinct tachycardias during programmed stimulation-directed testing of different antiarrhythmic drugs.[16] Thus, an assessment of reproducibility by the diversity in tachycardia configuration may be less clinically meaningful than a criterion based upon the ability to repeatedly induce a sustained ventricular arrhythmia.

The ideal protocol and end points for programmed stimulation are controversial.[17,18] Although our protocol used up to 4 extrastimuli, the frequency of induced sustained ventricular tachyarrhythmias was no greater than that observed in comparable studies using fewer extrastimuli.[19] VF was induced in 5 patients with nonreproducible arrhythmias, but 4 of these 5 patients (80%) had documented clinical VF. Recent work has supported the prognostic significance of inducible VF in such patients whose presenting clinical arrhythmia is VF.[20]

For those who might wish to assess the frequency of inducible and nonreproducible arrhythmias from fewer programmed extrastimuli, such data are provided in Figures 1 and 2. Of note, because inducibility and reproducibility are inversely related, stimulation protocols that result in fewer nonreproducible arrhythmias may also fail to identify inducible arrhythmias for which the patient remains at risk. Finally, if the induction of either sustained or nonsustained VT are regarded as equivalent end points during electrophysiologic testing, the frequency of nonreproducible arrhythmias (induction of either sustained or nonsustained VT versus at most 1 to 3 repetitive ventricular responses) would only diminish to 36% in group I (Table IV), and the overall conclusions of this study would remain unchanged.

Implications: Among patients with coronary artery disease, important day-to-day differences in rhythms provoked by programmed electrical stimulation are observed both in the drug-free state as well as when identical antiarrhythmic drugs at comparable therapeutic plasma concentrations are tested. This variability or "noise" within electrophysiologic testing is not readily attributable to the clinical arrhythmia, nor to the character of the arrhythmia (reproducible or nonreproducible) induced in the drug-free state. Drug trials directed by programmed electrical stimulation should therefore be cautiously interpreted because time-associated changes, alone, may mimic a change attributed to a beneficial or deleterious drug effect.

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Exaggerated Pressure Response to Exercise in Men at Risk for Systemic Hypertension

Michael F. Wilson, MD, Bong Hee Sung, PhD, Gwendolyn A. Pincomb, PhD, and William R. Lovallo, PhD

Normotensive persons at high risk of developing systemic hypertension have greater cardiovascular reactivity to mental and physical stressors. This study compared cardiovascular responses to exercise in normotensive men (aged 28 ± 0.8 years [mean ± standard error of the mean]) at high risk (positive parental history and high normal resting blood pressure [BP], n = 20) and at low risk (negative history, low normal BP, n = 15) of hypertension. All men had normal body weight and exercise tolerance. During graded supine bicycle exercise, 35% (7 of 20) of high-risk men had exaggerated BP responses (≥230/100 mm Hg) versus 0% of low-risk men, thus forming 3 groups (low risk, high-risk normal BP response, high-risk exaggerated response). Cardiac function was measured by nuclear cardiography. Cardiac index, peripheral resistance index, left ventricular ejection fraction and contractility index were measured at rest and during each exercise work load. High-risk exaggerated responders could not be distinguished from their high-risk normal-responding counterparts using resting BP or other cardiovascular variables. During exercise all 3 groups had equivalent increases in cardiac output. However, the high-risk exaggerated responders had blunting in peripheral resistance decline, resulting in excessive BP increases. This finding suggests an impaired capacity for exercise-induced vasodilation, indicating that the exaggerated response group may be at highest risk for future hypertension in these 3 groups.

(Am J Cardiol 1990;66:731–736)

This study evaluates and compares cardiac function and systemic vascular hemodynamics at rest and during exercise in normotensive young men who are either at low or high risk for hypertension. This risk was estimated based on parental history of hypertension and on the person's resting blood pressure (BP).

Persons with a parental history of hypertension are at higher risk of development of the disorder.[1,2] Elevated resting pressures within the normal range are also predictive of future hypertension.[3] However, assessment of BP based on resting values[4] has limitations in the early detection of permanent hypertension and for predicting the BP response to physical or mental activity.[5–7] Populations at higher risk of hypertension have greater cardiovascular reactivity to mental stress and to other stimuli.[6–8] It is not uncommon to find a hypertensive response during treadmill or bicycle exercise testing.[9,10] An exercise BP of ≥225/90 mm Hg as a predictor of future resting hypertension had a relative risk index of 2.3 over 32 months.[11] An increased ratio of systolic BP to heart rate seen with such pressures during moderate exercise suggests an impaired vascular response.[12,13]

During bicycle exercise we observed an exaggerated BP response (≥230/100 mm Hg) in 7 of 20 high-risk men (35%) and in none of the low-risk men. We report a comparison of resting and exercise cardiovascular dynamics in the 3 groups: low risk, high-risk normal exercise BP response, and high-risk exaggerated response. This delineation should improve our understanding of the enhanced neurogenic drive thought to occur in the early stages of essential hypertension.[14,15]

METHODS

Subjects: Thirty-five normotensive white men, aged 28 ± 0.8 years (mean ± standard error of the mean), who met the inclusion criteria for this study were designated either at high or low risk for development of essential hypertension. The high-risk group, consisting of 20 subjects, had a parental history of hypertension of either or both parents verified by a physician, and high-normal resting BP. This was defined as ≥2 resting BPs between 135 to 154 mm Hg systolic and 85 to 90 mm Hg diastolic, obtained after being seated upright for 5 minutes. The low-risk group (15 subjects) had a negative parental history and low normal resting BP ≤132/84 mm Hg.

All subjects signed a consent form approved by the combined Institutional Review Board of the University of Oklahoma Health Sciences Center and Veterans Af-

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TABLE I Subject Characteristics

Variable	All Subjects (n = 35)	Low Risk (n = 15)	High Risk (n = 20)	Low Versus High Risk	
				t	p
Age (yrs)	28 (0.8)	27 (1.2)	28 (1.2)	0.55	NS
Height (cm)	180 (1.2)	181 (1.9)	179 (1.7)	0.58	NS
Weight (kg)	79 (1.9)	75 (2.3)	82 (2.6)	1.85	0.08
Body fat (%)*	22 (0.7)	21 (0.8)	23 (1.0)	2.02	0.06
QI (g/cm^2)	2.43 (0.04)	2.29 (0.05)	2.53 (0.1)	3.34	0.01
Treadmill time (min)	14.8 (0.5)	14.9 (0.6)	14.6 (0.7)	0.35	NS
Blood Pressures at Phase 1 Screening After 5 Minutes†					
Systolic BP (mm Hg)	126 (1.9)	117 (2.2)	133 (1.8)	5.85	0.0001
Diastolic BP (mm Hg)	72 (1.5)	66 (2.3)	77 (1.3)	4.06	0.0005
Blood Pressures at Phase 1 Screening After 15 Minutes†					
Systolic BP (mm Hg)	124 (1.6)	116 (1.5)	130 (1.4)	6.74	0.0001
Diastolic BP (mm Hg)	72 (1.4)	68 (2.2)	75 (1.5)	2.70	0.02
Blood Pressures at Phase 2 Screening†					
Systolic BP (mm Hg)	123 (2.1)	113 (2.5)	129 (2.0)	5.05	0.0001
Diastolic BP (mm Hg)	78 (1.3)	73 (1.6)	82 (1.4)	4.24	0.0002

* Body fat based on skinfold thickness. Data were available for only 19 high-risk subjects.

† Entries show means of 3 readings over 5 minutes.

Values are mean ± standard error of the mean. Student's *t* test compares low- versus high-risk groups. Phase 1 blood pressures recorded by Critikon, Dynamap (Tampa, Florida) automated monitor. Phase 2 pressures were measured by auscultation using the disappearance of Korotkoff sounds as diastolic pressure.

BP = blood pressure; QI = Quetelet index.

TABLE II Subject Characteristics

Variable	Low Risk Normal	High Risk		p
		Normal	Exag.	
Age (yrs)	27 (1.2)	26 (1.4)	32 (1.6)	0.075
Height (cm)	181 (1.9)	181 (2.2)	176 (2.4)	NS
Weight (kg)	75 (2.3)	81 (3.7)	82 (3.4)	NS
Body fat (%)	21 (0.8)	23 (1.4)	25 (1.2)	0.065
QI (g/cm^2)	2.29 (0.04)	2.47 (0.07)	2.65 (0.07)	0.005
Treadmill time (min)	15.0 (0.6)	15.0 (0.9)	13.0 (0.6)	NS
Phase 1 Screening After 5 Minutes				
Systolic BP (mm Hg)	117 (2.2)	134 (2.1)	132 (3.4)	0.001
Diastolic BP (mm Hg)	66 (2.3)	76 (1.6)	77 (2.4)	0.009
Phase 1 Screening After 15 Minutes				
Systolic BP (mm Hg)	116 (1.5)	132 (1.3)	128 (3.3)	0.0001
Diastolic BP (mm Hg)	68 (2.2)	75 (1.8)	74 (3.1)	0.04
Phase 2 Screening				
Systolic BP (mm Hg)	113 (2.5)	128 (2.6)	132 (3.1)	0.0002
Diastolic BP (mm Hg)	73 (1.6)	82 (1.5)	82 (2.8)	0.0002

Values are mean ± standard error of the mean. Low risk, n = 15; high risk, normal, n = 13; high risk exaggerated, n = 7. See Table I for description of recording conditions.

p values based on analysis of variance.

Exag. = exaggerated; other abbreviations as in Table I.

fairs Medical Center and were paid for their participation.

Study protocol: Each subject had a medical history, physical examination, morphometric measurements, and a preliminary treadmill exercise test. The bicycle exercise sessions consisted of a rest period, isotope labeling of red blood cells, instrumentation and preexercise baseline measurements of cardiovascular parameters, followed by measurements during each stage of exercise.

Screening: Morphometric measurements included height, weight, skin caliper measurements for body fat estimates and calculation of the Quetelet index[16] to evaluate body type. Other inclusion criteria were: age 21 to 35 years, weight within 20% of the normal range defined by Metropolitan Life Insurance Company tables, absence of self-reported illnesses, no prior history or treatment for hypertension, no current use of prescription medication, and normal exercise tolerance by a symptom-limited treadmill exercise test using the Bruce protocol.

Bicycle exercise: During a 30-minute, supine rest period the subject's red blood cells were labeled in vitro with 25mCi of technetium-99m and reinjected. Cardiovascular variables were obtained during the baseline with the subject supine and his feet positioned on the ergometer pedals. The exercise sequence consisted of 3 minutes at each of the following work loads: 100, 200, 400, 600, 800, 1000 kpm or until exhaustion. All subjects were able to perform exercise up to 600 kpm (100 watts) inclusive.

Instrumentation and cardiovascular parameters: An automatic BP monitoring system (Paramed, Palo Alto, California) was used with the cuff placed on the right arm to record exercise systolic and diastolic BP. Two sets of BPs were recorded at the end of baseline and during each exercise level. BPs during screening were obtained by a Critikon Dinamap (Critikon, Tampa, Florida) monitor.

Cardiac images were obtained by multiple-gated nuclear ventriculogram[17,18] recorded for the last 2 minutes at each work load to obtain volumes and derived vari-

TABLE III Exercise Work Load (kpm)

Variable	Group	Rest	100	200	400	600
Systolic BP	Low	118 (2.0)	126 (2.8)	135 (2.4)	158 (3.9)	182 (3.9)
	Hi-N	130 (1.8)	137 (2.6)	145 (2.8)	158 (3.1)	183 (4.3)
	Hi-Ex	127 (2.8)	144 (5.0)	153 (6.4)	178 (7.7)	214 (9.9)
		*	*	*	*	*
Diastolic BP	Low	72 (2.0)	75 (2.2)	74 (1.8)	80 (2.1)	83 (3.0)
	Hi-N	78 (1.7)	82 (2.2)	81 (2.1)	80 (1.8)	86 (1.5)
	Hi-Ex	77 (3.3)	86 (3.6)	85 (2.5)	86 (2.5)	94 (3.6)
		†	†	†	†	†
Peripheral resistance index	Low	2652 (97)	1787 (93)	1563 (64)	1320 (77)	1114 (55)
	Hi-N	2821 (135)	1958 (121)	1757 (96)	1353 (77)	1209 (71)
	Hi-E	2889 (197)	2157 (188)	1898 (96)	1531 (70)	1347 (99)
		‡	‡	‡	‡	‡
Myocardial contractile index	Low	2.3 (0.12)	3.1 (0.2)	3.4 (0.2)	4.4 (0.3)	7.6 (1.2)
	Hi-N	3.1 (0.29)	4.8 (0.8)	6.1 (1.0)	8.5 (2.1)	22.7 (6.9)
	Hi-E	2.7 (0.42)	4.2 (0.7)	4.6 (0.7)	9.9 (3.4)	11.5 (3.0)
		‡	‡	‡	‡	‡
Systolic BP to heart rate ratio	Low	2.0 (0.06)	1.6 (0.3)	1.5 (0.2)	1.5 (0.3)	1.3 (0.2)
	Hi-N	2.1 (0.11)	1.6 (0.2)	1.6 (0.3)	1.4 (0.2)	1.3 (0.2)
	Hi-Ex	2.4 (0.15)	1.8 (0.3)	1.8 (0.4)	1.7 (0.3)	1.6 (0.3)
		‡	‡	‡	‡	‡
Cardiac index	Low	2.7 (0.09)	4.3 (0.2)	4.9 (0.2)	6.7 (0.4)	8.6 (0.4)
	Hi-N	2.8 (0.10)	4.3 (0.2)	4.9 (0.3)	6.5 (0.3)	8.1 (0.4)
	Hi-Ex	2.8 (0.14)	4.0 (0.2)	4.6 (0.1)	6.1 (0.2)	8.3 (0.8)
		NS	NS	NS	NS	NS

* $p < 0.01$; † $p < 0.05$; ‡ $p < 0.08$. Values are mean ± standard error of the mean.

Units: systolic and diastolic BP (mm Hg); peripheral resistance index (dynes · s · cm^{-5} · m^{-2}); myocardial contractile index (mm Hg/ml); systolic BP to heart rate ratio (mm Hg/beats/min); cardiac index (liters/min/m^2).

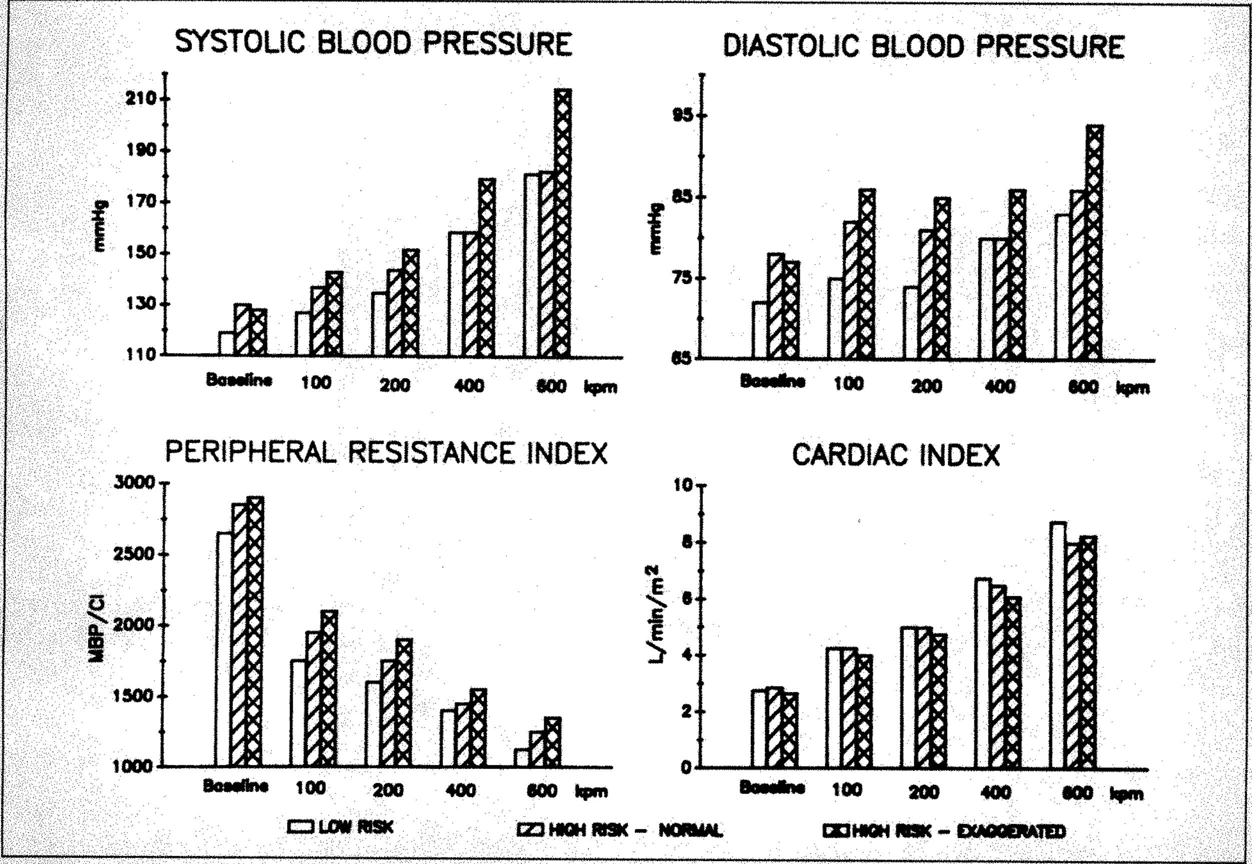

FIGURE 1. Hemodynamic measurements of 3 risk groups at baseline control and during mild to moderate bicycle exercise (100 to 600 kpm). CI = cardiac index; DBP = diastolic blood pressure; PRI = peripheral resistance index; SBP = systolic blood pressure.

ables. Cardiac parameters included left ventricular end-diastolic and end-systolic volumes, stroke volume and cardiac output. Volumes and cardiac output were converted to indexes by dividing by body surface area. Three additional cardiovascular parameters were calculated: peripheral resistance index as the ratio of mean blood pressure divided by cardiac index, left ventricular ejection fraction, and myocardial contractility assessed by the ratio of systolic BP to end-systolic volume. Whereas the ejection fraction response to bicycle exercise[19] is a standard measure of ventricular contractile performance, the systolic BP/end-systolic volume ratio is less affected by changes in preload or afterload conditions[20,21] and has proved to be a sensitive indicator of changes in cardiac function.[17]

Statistical analysis: High- and low-risk groups were compared for matching variables, morphometric characteristics, time on treadmill, and screening BP using Student's *t* test. These same variables were compared among low risk, high-risk normal exercise BP, and high-risk exaggerated BP groups using a 3-groups, 1-way analysis of variance (ANOVA).

Resting data were compared for the 2 risk groups using Student's *t* test and for the 3 groups using a 1-way ANOVA. Hemodynamic and cardiac activity at rest was represented as the average of 3 sets of supine measurements taken in the exercise position.

Exercise data were analyzed between the 2 risk groups for each dependent variable using 2 risk groups (low and high) × 4 exercise stage (100, 200, 400, 600 kpm) ANOVA with a repeated measure over the latter variable. The 3 groups were analyzed using a 3-group (low-risk, high-risk normal BP response, high-risk exaggerated) × 4 exercise stage repeated measure ANOVA.

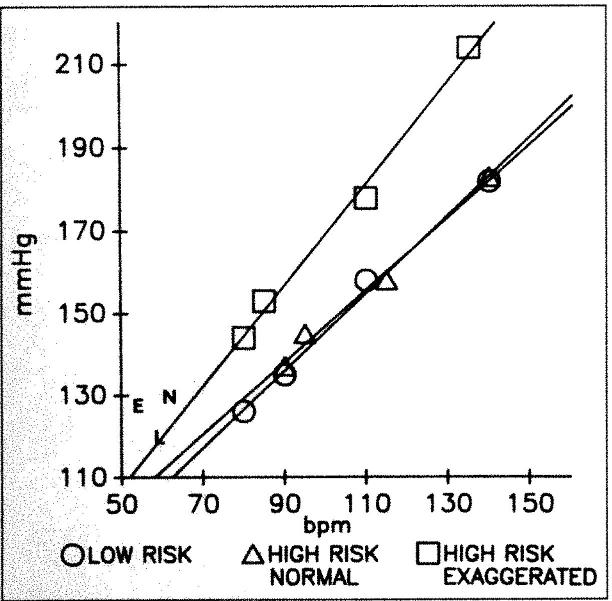

FIGURE 2. Relation between systolic blood pressure (SBP) and heart rate (HR) for the 3 risk (RSK) groups at rest and during graded bicycle exercise. EH = essential hypertension; E, EXG = exaggerated; L = low; N, NRM = normal.

ANOVA was conducted using the program BMDP, P2V (University of California at Los Angeles, Los Angeles, California). The criterion $p < 0.05$ was adapted for statistical significance.

RESULTS

The 2 risk groups (Table I) were not different in age, height and symptom-limited exercise treadmill time ($p > 0.05$). Subjects in the high-risk group tended to be heavier ($p < 0.08$) and to have more body fat based on skinfold measures ($p < 0.06$).[22] Their weight (g)/height (cm^2) ratio (QI)[17] was greater than that in the low-risk group ($p < 0.01$). Systolic and diastolic BPs measured at phase 1 screening were normal for both risk groups, although the high-risk group had increased BPs ($p < 0.001$) at both times and at phase 2 screening ($p < 0.05$). These higher resting systolic and diastolic BPs for the high-risk group were accompanied by a greater contractile activation ($p < 0.05$). This greater activation is also seen in a trend toward higher ejection fraction and lower end-systolic volume in the high-risk than in the low-risk group ($p < 0.08$). The risk groups did not differ in baseline heart rate, cardiac index, end-diastolic volume or peripheral resistance.

Comparison of the risk groups during exercise showed that the differences seen at rest remained for systolic and diastolic BPs, contractile index ($p < 0.05$) and ejection fraction ($p < 0.08$). This suggests a durable characteristic which remained during exercise. There was also a tendency for peripheral resistance to remain higher during exercise in the high-risk group ($p < 0.08$), thus presenting a consistently elevated resistance at each given exercise work load compared with the low-risk group. However, the apparently greater systolic activation of the high-risk group, indicated by greater contractile index and ejection fraction, did not translate into a higher cardiac output. Features of a greater afterload with the same cardiac output indicate a greater cardiac work load in the high-risk group and suggest a possible reason for the systolic activation. All 15 low-risk subjects had a normal BP response to exercise. In the high-risk group 7 of the 20 subjects (35%) had an exaggerated (hypertensive) BP response (≥230/100 mm Hg) at or before maximal exercise work load. One high-risk subject had this exaggerated response at the lowest work load (100 kpm), and the other 6 did so at the moderate work load of 600 kpm (100 watts).

Given this remarkable separation of BP response to exercise between the low- and high-risk groups, we could now identify a third risk group which was characterized not only by positive parental history for hypertension and high normal resting BP, but also by an exaggerated or hypertensive BP response to exercise. The question now was whether this third group differed in other characteristics from the normotensive exercise responders. Those with an exaggerated BP response averaged 5 to 6 years older ($p < 0.075$) and had a significantly greater weight-to-height ratio ($p < 0.005$) (Table II). Their resting systolic and diastolic BPs were significantly different from those in the low-risk group but not from BPs in the normotensive responders in the high-risk group. This was true for both phases of screening (Table II).

In comparing the resting hemodynamic values of subjects who had an exaggerated BP response to exercise with the high-risk normotensive responders, there were no distinguishing features in terms of BP, peripheral resistance, cardiac index or myocardial contractility, although the ratio of systolic BP to heart rate was directionally greater in the group with exaggerated BP (Table III).

During exercise, the exaggerated responders were characterized by greater systolic and diastolic BPs, and greater systolic BP to heart rate ratio, but cardiac index and contractility were less than the normotensive responders (Table III, Figure 1). Examination of peripheral resistance revealed that high-risk exaggerated responders maintained directionally higher levels of resistance at all stages of exercise ($p < 0.08$) (Table III, Figure 1).

The exaggerated BP response group showed a different relation between systolic BP and heart rate across exercise work loads (Figure 2). The slope of the systolic BP/heart rate ratio during exercise was greater ($p < 0.05$) in the exaggerated responders than in the normotensive response groups, indicating a heightened systolic BP elevation for a given increment in heart rate. This is consistent with the latter group having an increased vascular tone during exercise.

The systolic and diastolic BP characteristics of the 3 risk groups before, during and after treadmill exercise are depicted in Figure 3. Resting pressures were the same in the 2 high-risk groups whether the subjects were supine, sitting or standing, and were, therefore, not modified by postural reflexes. During exercise there was a statistically significant separation of systolic and diastolic BPs among the 3 groups ($p < 0.001/0.01$). In both low-risk and high-risk normal responders diastolic BP tended to decline during exercise but failed to do so in the high-risk exaggerated response group. During recovery, with the subjects sitting, diastolic BP in the high-risk exaggerated response group showed a sustained level in contrast to the normal decrease seen in the other 2 groups. While only heart rate and BP were recorded during treadmill exercise, the changes during exercise and recovery are consistent with a pattern of reduced vascular depressor response to metabolic and/or neurohormonal vasodilator substances in the high-risk exaggerated response group. On the other hand, this response appeared to be normal in the normotensive responders as documented by the decrease in diastolic BP during exercise and recovery (Figure 3).

DISCUSSION

Although exercise has been studied in hypertensives and borderline groups,[8,13,23] there has been a lack of work in high-risk normotensives. Our most general finding is that high-risk men had a persistent elevation of BP across several stages of exercise. They appeared to show normal cardiovascular regulation and did not differ from the low-risk group in the form of their response to exercise.

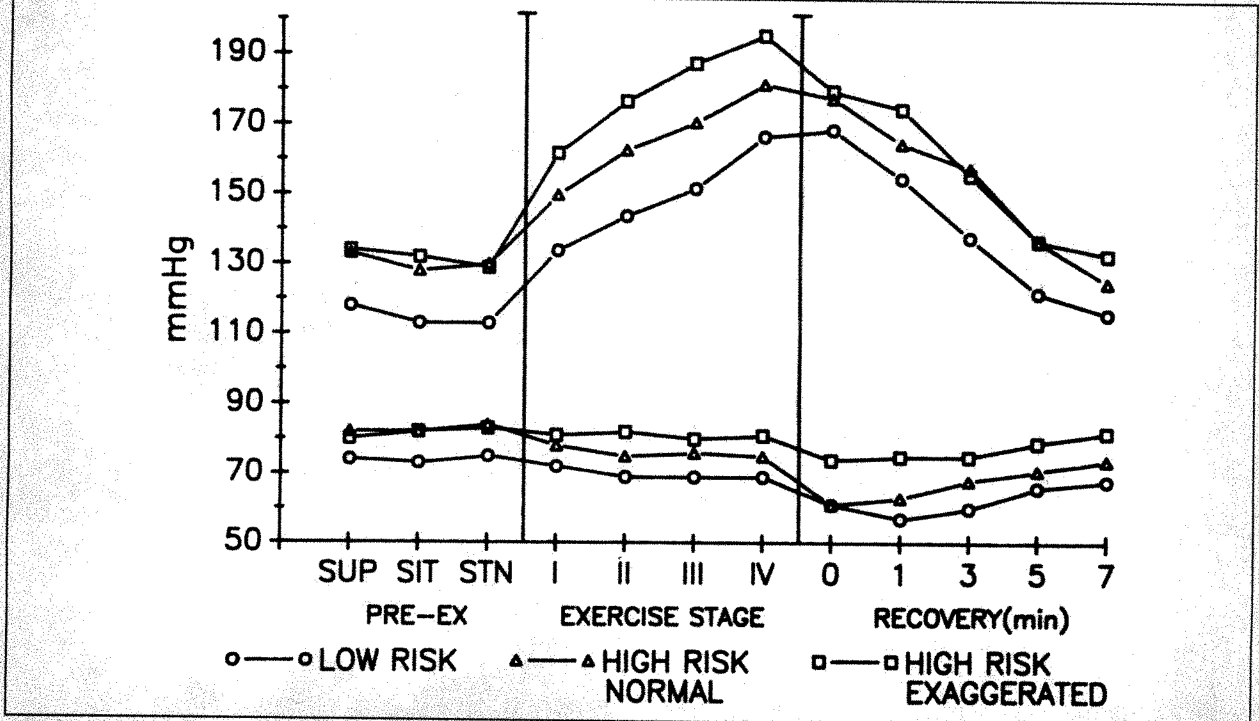

FIGURE 3. Comparison of systolic and diastolic blood pressures (BP) and response patterns of the 3 risk groups to changes in posture, treadmill exercise and recovery. LORSK = low risk group; SIT = sitting; STN = standing; SUP = supine. Other abbreviations as in Figure 2.

However, a significant subgroup of the high-risk men (35%) had an exaggerated BP response to exercise. When examined as a separate subgroup, these men had a dysregulation of vascular function during exercise seen as an attenuated vasodilation response relative to their high-risk counterparts. In contrast, they had the same increase in cardiac output as the other groups. The net effect was that BP increased disproportionately with exercise work load. This deregulation is illustrated in a steeper increase in systolic BP for each increment in heart rate. Finally, the same trends in BP deregulation were seen during treadmill exercise. These findings suggest that among high-risk normotensive men, there may be a subset which manifests poor vascular regulation to exercise and which may be at higher risk than their matched counterparts.

Most prior studies have employed invasive techniques at rest and exercise that may have produced anxiety resulting in elevated cardiac output and reduced vascular resistance. This pattern is frequently observed during behavioral states requiring enhanced attention and performance and is part of a classic alerting response.[24] Borderline hypertensives may show more pronounced changes than normotensives.[15] Noninvasive measurement techniques of cardiac function and cardiovascular dynamics as used here have become quite accurate[18] and reproducible,[25] and offer an important advantage in obtaining true resting values by limiting the element of anxiety that may activate centrally mediated cardiac and vascular responses.[26]

With regard to the prognostic value of exercise BP, several observations seem pertinent. In a retrospective review of 4,856 patients undergoing exercise testing, 1.1% had an exaggerated response (systolic/diastolic BP ≥230/110 mm Hg).[10] There was no difference in systolic pressure between bicycle and treadmill exercise, suggesting that the features of this response may be brought out by either type of exercise. The moderate work load of up to 100 watts (600 kpm) of exercise appears to be sufficient for the detection of exercise-induced hypertensive response.[6,23,27] In this regard all of our subjects who had an exaggerated BP response did so at or before this moderate exercise level. These hyperreactors to exercise had no differences at rest in BP, vascular resistance, cardiac output or contractility indexes from their high-risk counterparts who responded normally to exercise. Thus, this response pattern could not be predicted from the aforementioned baseline data. In this sense the present findings may indicate that resting BP is limited as an indicator of future hypertension risk and that stress-related measures may have more prognostic value.

The response pattern of the high-risk exaggerated response group suggests a generally stable characteristic consisting of an impairment of cardiovascular adjustment to exercise which is not apparent at rest and which may indicate a greater risk for the development of future essential hypertension. Frequent hemodynamic stress of the magnitude demonstrated in this study in hypertensive high-risk subjects could constitute an additional risk factor for the development of left ventricular hypertrophy and accelerated target organ damage.

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Factors Influencing Progression of Mitral Regurgitation After Transarterial Balloon Valvuloplasty for Mitral Stenosis

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This study analyzes the clinical, echocardiographic and hemodynamic factors affecting progression of mitral regurgitation (MR) after transarterial balloon valvuloplasty in 200 consecutive patients with rheumatic mitral stenosis. After valvuloplasty, the mitral valve area increased in all patients, from 1.03 ± 0.36 to 2.06 ± 0.71 cm^2 ($p < 0.0001$). With regard to the basal stage, the mitral valve was competent in 139 patients and there was mild MR in 61 (grade I in 53, and grade II in 8). Three patients had progression of MR induced by a technical deficiency and they were excluded from analysis. Patients were classified into 2 groups on the basis of the degree of MR before and after valvuloplasty: group A—no progression of MR ($n = 167$; 85%) when the degree of MR did not change, disappeared after valvuloplasty, or increased from grade 0 to I; group B—progression of MR ($n = 30$; 15%) when the degree of MR increased to $\geq$ grade II. Progression of MR was observed more frequently in older patients with presence of chronic atrial fibrillation, larger left atrial size and left ventricular volumes, baseline MR, more severe stenosis and a lower ejection fraction. Multivariate analysis selected age, left ventricular volumes and ejection fraction as independent predictors of progression of MR. All these factors suggest that progression of MR after balloon valvuloplasty could be related to a more advanced degree of disease.

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Percutaneous mitral valvuloplasty has recently been developed as an alternative to surgical treatment in patients with rheumatic mitral stenosis. Preliminary reports have shown favorable early and midterm hemodynamic results.[1-14] The mechanism of dilation is based mainly on the splitting of the fused commissures,[1,4,5,8] which can lead (as occurs in surgical commissurotomy) to a different degree of progression of mitral regurgitation (MR). In addition to technical considerations, factors influencing progression of MR after balloon valvuloplasty are not well known.[6,7,11,15] The present study analyzes clinical, echocardiographic and hemodynamic factors affecting progression of MR after valvuloplasty in 200 patients with rheumatic mitral stenosis.

METHODS

Patients: The study included the first 200 patients enrolled in a cooperative study who presented with symptomatic mitral stenosis and were treated by transarterial balloon valvuloplasty. All patients underwent clinical and echocardiographic studies before and after valvuloplasty. Pliability was defined as minimal or no restriction of the leaflet mobility, absence of significant thickening or calcium at the leaflets, and minimal or no subvalvular disease. Before and after dilation, hemodynamic measurements and a left ventricular angiogram (single-plane 30° right anterior oblique projection) were obtained. Cardiac output was measured using thermodilution or dye-dilution technique. The left ventricular angiogram was carefully inspected to quantify the volumes, ejection fraction and the degree of subvalvular fibrosis by the "distance-ratio" measurement.[16] Severity of MR was graded qualitatively from 0 to IV. The presence of mitral valve calcium was identified by fluoroscopy. Angiographic follow-up evaluation was available in 39 patients at a mean period of 20 ± 7 months after dilation.

Baseline characteristics: The study included 151 women and 49 men aged 16 to 73 years (mean ± standard deviation 45.2 ± 12.3); 68 patients were in New York Heart Association functional class II, 122 in class III and 10 in class IV; 92 patients (46%) had atrial fibrillation and 42 had undergone a previous surgical commissurotomy. The mitral valve was considered pliable in 84 (42%), fibrotic in 86 and calcified in 30 as

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evaluated by echocardiography. Mean size of the left atrium was 50.7 ± 8.4 mm. Angiographically, the mitral valve was competent in 139 patients, there was MR grade I in 53 and grade II in 8. The valve, seen by fluoroscopy, was calcified in 52 patients (26%). The mean distance-ratio was 0.16 ± 0.05. One patient had coronary artery disease.

Procedure: We always performed a retrograde transarterial approach as described by Babic et al.[2] After transseptal puncture all patients were given intravenous heparin; then, a flow-directed catheter was inflated with carbon dioxide and advanced into the apex of the left ventricle, and then across the aortic valve into the ascending aorta. Through this catheter, a long exchange guidewire was passed into the ascending aorta and was snared and exteriorized through the left femoral artery by a retrieval catheter. Sixteen patients had an associated aortic valve stenosis that was sequentially dilated during the same procedure.[17] Balloon size selection was always based on echocardiographic and angiographic measurements of the mitral anulus. The ratio mitral anulus diameter/balloon size was 1.15 ± 0.15 (range 0.84 to 1.47).

Definitions: Patients were classified into 2 groups on the basis of the degree of MR before and after valvuloplasty. Group A consisted of patients with no progression of MR (n = 167; 85%) when the degree of MR did not change after valvuloplasty, disappeared or increased from grade 0 to I. Five patients having MR grade II in the basal condition persisted with no change after valvuloplasty, and were not considered to progress. Group B consisted of patients with progression of MR (n = 30; 15%) when the degree of MR increased to ≥ grade II (Figure 1). At the beginning of our experience, 3 patients had progression of MR induced by a technical complication due to a bad positioning of the balloon, and they were excluded from analysis; in 2 of them, MR progressed to grade III and in 1 to grade IV.

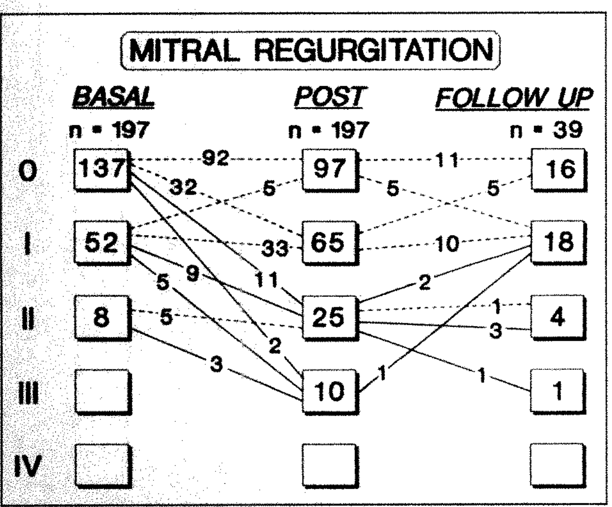

FIGURE 1. Angiographic changes observed in the degree of mitral regurgitation immediately after balloon valvuloplasty in 197 patients and at follow-up in 39 patients. *Dotted lines*, group A (no progression); *straight lines*, group B (progression).

Statistical analysis: The analyzed parameters are listed in Table I. Data are presented as mean ± standard deviation. A chi-square test was used to assess the difference in categoric variables. Unpaired Student's t test was used to assess differences in continuous variables between patients in both groups. A p value <0.05 was considered indicative of statistical significance. From the subset of patients from which a complete set of data was available (n = 143), a multivariate analysis was performed using stepwise logistic regression analysis to determine the independent predictors of progression of MR. Only variables achieving univariate statistical significance at the level $p < 0.05$ were entered into the multivariate analysis to minimize the problem of comparison of multiple variables.

RESULTS

Global results: After valvuloplasty the mean mitral gradient decreased significantly from 17.2 ± 7.2 to 5.7 ± 3.7 mm Hg ($p < 0.0001$). There were no significant changes in cardiac output (4.33 ± 1.13 to 4.47 ± 1.28 liters/min). The mitral valve area increased from 1.03 ± 0.36 to 2.06 ± 0.71 cm^2 ($p < 0.0001$). Left atrial pressure was significantly reduced, from 23.1 ± 7.8 to 12.5 ± 6.9 mm Hg ($p < 0.0001$). The basal ejection fraction was 0.56 ± 0.09 (range 0.30 to 0.75) and was unchanged after valvuloplasty. Left ventricular end-diastolic and end-systolic volume indexes also were not significantly modified after valvuloplasty.

Mitral regurgitation: Figure 1 shows the changes observed in the degree of MR immediately after valvuloplasty and at follow-up. In 32 patients MR increased from grade 0 to I, which was not considered a significant progression. In 130 patients (66%) the degree of MR did not change. In 5 patients with grade I in the basal stage, MR disappeared after the procedure. There was significant progression of MR in 30 patients (15%), as previously defined (≥ grade II). Angiographic follow-up in 39 patients (32 from group A [19%] and 7 from group B [23%]) showed that in 8 patients (21%) the degree of MR decreased, and in 25 (64%) that degree did not change. These minor changes were observed in both groups, but no patients from group A progressed to ≥ grade II at follow-up.

Predictors of progression of mitral regurgitation: The univariate analysis of factors influencing progression of MR are listed in Table I. There were no significant differences between both groups in terms of gender, previous commissurotomy and the status of the mitral valve as characterized by echocardiographic and angiocardiographic examination. The mean size of the balloon and the anulus/balloon ratio was similar in both groups. However, progression of MR was significantly associated with an older age, a higher incidence of chronic atrial fibrillation, a lower basal stage and the presence of baseline MR. Additionally, progression of MR was also associated with larger left atrial and ventricular size, as characterized by left atrial diameter and left ventricular volumes. Similarly, ejection fraction was significantly lower in patients who had progression of MR. The multivariate analysis (Table II) selected the

TABLE I Factors Influencing Progression of Mitral Regurgitation (Univariate Analysis)

	No Progress (n = 167)		Progress (n = 30)
Clinical			
Age (yrs)	44.4 ± 12.2	—*—	49.0 ± 11.3
Sex (% female)	77%		70%
Atrial fibrillation	41%	—†—	72%
Previous commisurotomy	21%		31%
Echocardiographic			
"DE" amplitude (mm)	17.8 ± 4.5		16.7 ± 6.0
"EF" slope (mm/sec)	14.1 ± 8.0		11.5 ± 8.2
Left atrial diameter (mm)	49.9 ± 8.1	—*—	54.3 ± 9.0
Flexibility (% pliable)	44%		33%
Hemodynamics			
Mild mitral regurgitation	26%	—†—	57%
Mild aortic regurgitation	37%		40%
Subvalvular fibrosis (DR)	0.16 ± 0.05		0.16 ± 0.05
Calcium (fluoroscopic)	25%		34%
Basal gradient (mm Hg)	17.0 ± 7.0		18.8 ± 8.3
Basal area (cm^2)	1.06 ± 0.37	—†—	0.87 ± 0.25
Cardiac output (liters/min)	4.46 ± 1.11	—‡—	3.64 ± 0.96
Ejection fraction	0.57 ± 0.08	—‡—	0.51 ± 0.09
EDVI (ml/m^2)	100 ± 31	—†—	117 ± 34
ESVI (ml/m^2)	44 ± 18	—†—	57 ± 19
Mitral anulus angio (mm)	38.8 ± 5.2		41.0 ± 5.4
Balloon diameter (mm)	34.2 ± 4.0		35.2 ± 3.9
Anulus/balloon ratio	1.14 ± 0.15		1.16 ± 0.14

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.
Angio = angiography; DR = distance-ratio; EDVI = end-diastolic volume index; ESVI = end-systolic volume index.

TABLE II Factors Influencing Progression of Mitral Regurgitation (Multivariate Analysis)

	Regression Coefficient	Standard Error	p
ESVI	0.219	0.081	0.003
Ejection fraction	0.326	0.106	0.011
Age	−0.053	0.026	0.045
EDVI	−0.115	0.037	0.048
Constant	−11.625	5.872	—

Abbreviations as in Table I.

age, left ventricular volumes and ejection fraction as independent predictors of progression of MR.

DISCUSSION

Regardless of the absence of technical mistakes during the procedure, MR may progress in different degrees after balloon dilatation.[1-15] The causes of that progression are not known. Until now, only anatomic descriptions of the valve were available from surgical findings in patients with severe MR after balloon valvuloplasty.[6,14] They showed tears and detachment of the leaflets and/or damage of the subvalvular apparatus. However, minor degrees of MR would probably have a different mechanism.[7,11,13] Only few studies[3,7,14,15] have investigated the determinants of progression of MR after valvuloplasty. The group from Boston, having had no success in detecting significant predictors of progression in 2 previous reports[3,7] ultimately found that a higher ratio of effective balloon dilating area to body surface area can influence progression of MR.[15] In our series, we always tried to adjust the balloon size to the angiographically measured mitral diameter. Consequently, this factor could not be identified in our study. However, Nobuyoshi et al[14] reported that the only significant predictor of progression of MR was the anatomic characteristics of the mitral valve according to echocardiography. Our findings did not confirm this. In fact, none of our parameters evaluating valve anatomy were significant predictors of progression of MR. Although the incidence of progression of MR is quite different between studies, these discrepancies might be explained by differences among the studies in terms of technique, definition of progression of MR and diagnostic methods in evaluating MR. Our analysis is characterized by a larger number of patients in an angiographically based study and by excluding those patients who developed progression of MR because of technical deficiencies. In addition, patients having no MR during basal conditions, in whom MR progressed to grade I after valvuloplasty, were not considered as having significant progression. That kind of progression is not clinically relevant and may even be a temporary phenomenon, not comparable to progression to ≥ grade II. Midterm follow-up studies have shown decreases in MR in about 50% of patients.[10,11,13,15] Our findings in 39 patients also have shown that in 5 of 15 patients (33%) with grade I MR after valvuloplasty, the valves became competent at follow-up. Thus, minor changes occur and progressions from grade 0 to I or regressions from grade I to 0 were frequently seen after valvuloplasty and at follow-up. This makes the study of progression of MR difficult and explains the different definitions used for progression.[3,7,14,15]

With our design, the analyzed anatomic features of the valve did not predict progression of MR. However, an older age, a higher ventricular size and a lower ejection fraction were independent predictors of progression of MR after balloon valvuloplasty. All these factors probably indicate a more advanced state of rheumatic disease as the main cause of that progression, and should be taken into account before indicating balloon valvuloplasty.

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Diagnostic Accuracy of Right Ventriculography in Arrhythmogenic Right Ventricular Cardiomyopathy

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Diagnostic sensitivity and specificity of cineangiography were evaluated by multivariate logistic discriminant analysis in 32 patients with arrhythmogenic right ventricular (RV) cardiomyopathy, 27 patients with biventricular dilated cardiomyopathy, 28 patients with atrial septal defect and 18 normal subjects. In patients with arrhythmogenic RV cardiomyopathy and biventricular dilated cardiomyopathy, the diagnosis was confirmed by endomyocardial biopsy. All RV values overlapped for the diagnosis of atrial septal defect and arrhythmogenic RV cardiomyopathy; overlapping extended to dilated cardiomyopathy for end-diastolic volume and infundibular dimensions. RV ejection fraction appeared reduced in all the diseases; in particular, mean values in dilated cardiomyopathy and arrhythmogenic RV cardiomyopathy were 38 and 53%, respectively ($p < 0.05$). Left ventricular quantitative studies showed a significant difference between dilated and arrhythmogenic RV cardiomyopathy, both in terms of pumping indexes (mean end-diastolic volumes 180 vs 91 ml/m^2 and mean ejection fraction 33 vs 60%), and indexes of contractility (stress/end-diastolic volume 3.7 vs 6.7).

Multivariate analysis disclosed that transversally arranged hypertrophic trabeculae, separated by deep fissures, were associated with the highest probability of arrhythmogenic RV cardiomyopathy ($p < 0.001$). Posterior subtricuspid and anterior infundibular wall bulgings were the only other independently significant variables. Coexistence of these signs was associated with 96% specificity and 87.5% sensitivity.

Thus, arrhythmogenic RV cardiomyopathy presents quantitative volumetric and hemodynamic as well as qualitative features that clearly distinguish it from dilated cardiomyopathy and confirm its nosographic autonomy among the primary diseases of the myocardium.

(Am J Cardiol 1990;66:741–745)

Cineangiographic investigation is currently used as a diagnostic procedure in evaluating patients with arrhythmogenic right ventricular (RV) cardiomyopathy.[1] This gives information about the functional and morphologic status of the cavities and parietal walls. Cardiomegaly, deep fissures, margin changes, localized akinetic or dyskinetic bulges, out-pouchings, dilatation of the infundibulum and slow dye evacuation are the most frequently reported diagnostic angiocardiographic parameters in previous reports.[2-4] These signs were associated with adipose or fibroadipose substitution of the RV walls, but information confirming their prevalence among patients with different RV pathologies is lacking. Furthermore, no attempt has been made to attribute diagnostic specificity and sensitivity to them. To determine their prevalence and evaluate their diagnostic value, we compared cineangiographic measurements and signs in patients with arrhythmogenic RV cardiomyopathy, biventricular dilated cardiomyopathy, atrial septal defect and in normal subjects.

METHODS

Cineangiograms of the right and left ventricles were analyzed qualitatively and quantitatively in 4 groups of patients, defined as follows: arrhythmogenic RV cardiomyopathy (32 patients, 16 males, 16 females; mean age 36, range 6 to 63 years); biventricular dilated cardiomyopathy (27 patients, 21 males, 6 females; mean age 43, range 19 to 66); atrial septal defect, ostium secundum type (28 patients, 16 males, 12 females; mean age 28, range 1 to 67); normal subjects (18 patients, 12 males, 6 females; average age 51, range 15 to 68).

The diagnosis of arrhythmogenic RV cardiomyopathy was formulated in patients with ventricular arrhythmias with a left bundle branch block morphology and abnormal T wave in precordial leads, on the basis of 2-dimensional echocardiographic documentation of localized or diffuse structural and dynamic anomalies involving exclusively or specifically the RV (regional wall motion abnormalities, such as hypokinesia, akinesia and dyskinesia and disarrangement of the trabecular pattern, with a hyperechogenic aspect of the muscular trabeculae), in the absence of valve disease, shunts, active myocarditis, coronary disease or pulmonary hypertension.

The diagnosis of biventricular dilated cardiomyopathy was made on the basis of clinical, radiologic, echocardiographic and hemodynamic findings of primary cardiomegaly with severe decrease in contractility.

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TABLE I Quantitative Evaluation of the Right and Left Ventricle (Mean Values)

Parameters	ARVC n = 32	DC n = 27	ASD n = 28	NS n = 18
EDV-RV (ml/m^2)	131^{B}	165^{A}	141^{B}	95^{C}
ESV-RV (ml/m^2)	62^{B}	104^{A}	66^{B}	38^{C}
EF-RV (%)	53^{B}	38^{C}	54^{B}	60^{A}
Infundibular diameter (cm)	5^{B}	6^{A}	5^{B}	2^{C}
Longitudinal axis (cm)	12^{B}	14^{A}	12^{B}	5^{C}
Infundibular diameter/ longitudinal axis	0.41^{B}	0.42^{B}	0.37^{C}	0.48^{A}
EDV-LV (ml/m^2)	91^{B}	180^{A}	75^{B}	79^{B}
EF-LV (%)	60^{B}	33^{C}	67^{A}	71^{A}
Mass/EDV-LV	0.99^{B}	0.83^{C}	1.01^{B}	1.25^{A}
Stress/ESV-LV	6.69^{B}	3.72^{C}	9.25^{A}	7.87^{B}
EDV-RV/EDV-LV	1.52^{C}	0.99^{B}	2.05^{BC}	1.22^{A}
EF-RV/EF-LV	0.88^{A}	1.23^{B}	0.80^{B}	0.84^{B}

Statistical significance of mean value differences among groups is marked by letters. Means marked with the same letter are not statistically significant ($p > 0.05$). Means marked with different letters are significantly different from p values <0.05.

ARVC = arrhythmogenic right ventricular cardiomyopathy; ASD = atrial septal defect; DC = dilated cardiomyopathy; EDV-LV = end-diastolic volume left ventricle; EDV-RV = end-diastolic volume right ventricle; EF-LV = ejection fraction left ventricle; EF-RV = ejection fraction right ventricle; ESV-LV = end-systolic volume left ventricle; ESV-RV = end-systolic volume right ventricle; NS = normal subjects.

In both arrhythmogenic RV cardiomyopathy and biventricular dilated cardiomyopathy, the diagnosis was confirmed by RV endomyocardial biopsy; the histologic picture of arrhythmogenic RV cardiomyopathy was characterized by more or less pronounced features of myocardial atrophy due to lipomatosis or fibrolipomatosis, while that of biventricular dilated cardiomyopathy showed myocytes of varying diameter, sarcolysis, nuclear hyperchromia and variation in size, with perinuclear halos and interstitial fibrosis.

Ostium secondum-type atrial septal defect was diagnosed by passing a catheter from the right to left atrium and oxymetric and angiographic findings of a left-to-right shunt through the interatrial septum.

The group of normal subjects was made up of patients with no abnormalities on electrocardiogram, chest x-ray, echocardiography and cardiac catheterization. These examinations were performed to evaluate pseudoangina pain or because congenital heart disease was suspected.

The following quantitative RV parameters were calculated in each group: end-diastolic volume, according to the surface-length method; end-systolic volume; ejection fraction; infundibulum diameter and ventricular longitudinal axis (the segment between the superior border of the tricuspid anulus and the ventricular apex, measured on a diastolic frame).[2] Regional kinetics were studied by qualitative analysis of the RV wall (apex, anterior free wall, diaphragmatic wall). Attention was addressed to end-diastolic bulging of the diaphragmatic and subtricuspid regions and the infundibular anterior wall; the prevalent trabecular arrangement (longitudinal, transverse) was noted, as well as the presence of transversally arranged hypertrophic trabeculae separated by deep fissures and coarse trabeculae in the apical region (mammilations). RV trabeculae were considered hypertrophic when angiocardiography disclosed a thickness ≥4 mm. Cases in which dye persisted in the right ventricle, beyond the duration of levophase, were also recorded, as well as the presence or absence of tricuspid valve leaflet prolapse.

In the left ventricle, end-diastolic volume (according to the monoplanar method of Green), ejection fraction, mass, mass/end-diastolic volume and stress/end-systolic volume, as well as ventricular kinetics and mitral valve morphology, were assessed. In all the patients, except those with atrial septal defect, selective coronary angiography was performed and coronary artery disease was ruled out. Left ventricular mass and stress were determined as described by Kennedy[5] and Falsetti[6] and their co-workers, respectively.

Statistical analysis: Qualitative parameters were initially examined separately by 2 observers and subsequently discussed by ≥3 observers.

One-way analysis of variance was used to explore the relation between continuous variables and the diagnostic class. Comparison of mean values among different classes was made according to the Bonferroni, Duncan and Scheffe tests.[7] Categorical variables were tabulated as contingency tables and their relation with each diagnostic group was examined by the chi-square test. To predict the occurrence of arrhythmogenic RV cardiomyopathy, a multiple regression of the discriminate function was performed in the logistic domain. A stepwise algorithm was used to select predictor variables.

Both continuous (age, end-diastolic volume, end-systolic volume, ejection fraction) and categorical variables were simultaneously analyzed. The categorical variables

TABLE II Significant Angiocardiographic Qualitative Parameters of the Right Ventricle

	ARVC n = 32	DC n = 27	ASD n = 28	NS n = 18	p Value
Apex dyskinesia	41%	7%	0	0	<0.0001
Tricuspid prolapse	41%	7%	22%	0	<0.001
Diaphragmatic dyskinesia	28%	7%	0	0	<0.0005
Bulging infundibular anterior wall	75%	11%	18%	11%	<0.0001
Bulging subtricuspid region	91%	56%	14%	5%	<0.0001

Chi-square test with 2 degrees of freedom (arrhythmogenic RV cardiomyopathy vs other diseases).
Abbreviations as in Table I.

were coded as follows: sex, 1,2; RV kinetics of the apex, 1 to 3 (hypo-, a-, dyskinesia), anterior wall, 1 to 3, diaphragmatic region, 1 to 3, global kinetic score, 1 to 9; subtricuspid bulging, 0 to 1; anterior bulging, 0 to 1; contrast, 0 to 1; trabecular mammilations, 0 to 1; tricuspid prolapse, 0 to 1; mitral prolapse, 0 to 1; transverse trabeculae plus deep fissures, 0 to 1; hypertrophic transverse trabeculae, 0 to 1; longitudinal trabeculae, 0 to 1; hypertrophic transverse trabeculae plus deep fissures, 0 to 1; trabecular thickness, 1 to 4; left ventricle kinetics, 1 to 3; and global kinetic score, 1 to 9.

Variables with a p value <0.05 were allowed in the model. The discriminant power of the most significant variables was explored with classification tables and a parsimonius model, choosing the most significant decrease of logarithmic likelihood and the highest rate of predictions.

RESULTS

Table I lists the values of cineangiographic quantitative evaluation of the right and left ventricles in the 4 diagnostic groups.

Right ventricle: The quantitative parameters were significantly increased in all the categories, compared to the group of the normal subjects. Analysis of variance disclosed that all parameters overlapped for the diagnosis of atrial septal defect and arrhythmogenic RV cardiomyopathy. This overlapping extended to biventricular dilated cardiomyopathy for end-diastolic volume and infundibular dimensions.

Left ventricle: Biventricular dilated cardiomyopathy patients differed from the others due to the high end-diastolic volume values and the important impairment in the indexes of pumping and contractility. In the remaining 3 groups, values tended to overlap at the upper and lower confidence limits and the lowest values were observed in arrhythmogenic RV cardiomyopathy.

Table II lists the angiocardiographic qualitative parameters of the RV and discloses significant differences in patients with arrhythmogenic RV cardiomyopathy. These patients showed a higher rate of dyskinesia of the apex (41%) and diaphragmatic wall (28%); end-diastolic bulging of the infundibular anterior wall and subtricuspid region were found in 75 and 91% of our cases, respectively. Tricuspid valve prolapse was significantly more frequent in the arrhythmogenic RV cardiomyopathy group (41%) compared to biventricular dilated cardiomyopathy (22%) and atrial septal defect (7%). The presence of mammilations of the RV walls or dye persistence during levophase did not vary among the groups; transverse or longitudinal type arrangement of the trabeculae and their thickness also showed no differences.

Discriminant analysis disclosed that transversally arranged hypertrophic trabeculae separated by deep fissures (Figure 1) was the qualitative variable most significantly associated with arrhythmogenic RV cardio-

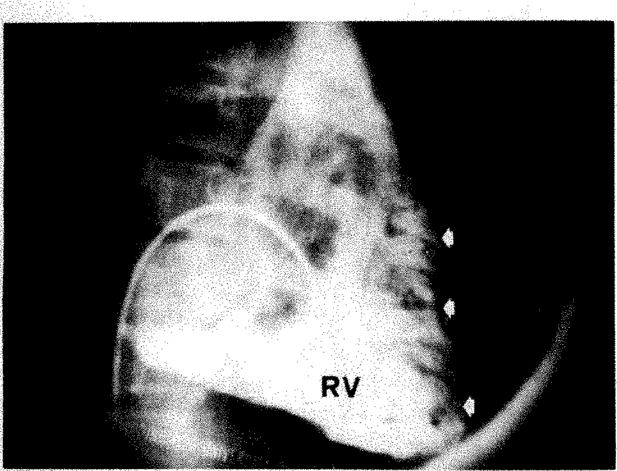

FIGURE 1. Angiocardiography of right ventricle (RV), end-diastolic right anterior oblique (long-axis) view: hypertrophic trabeculae arranged transversally and separated by deep fissures *(arrows)*.

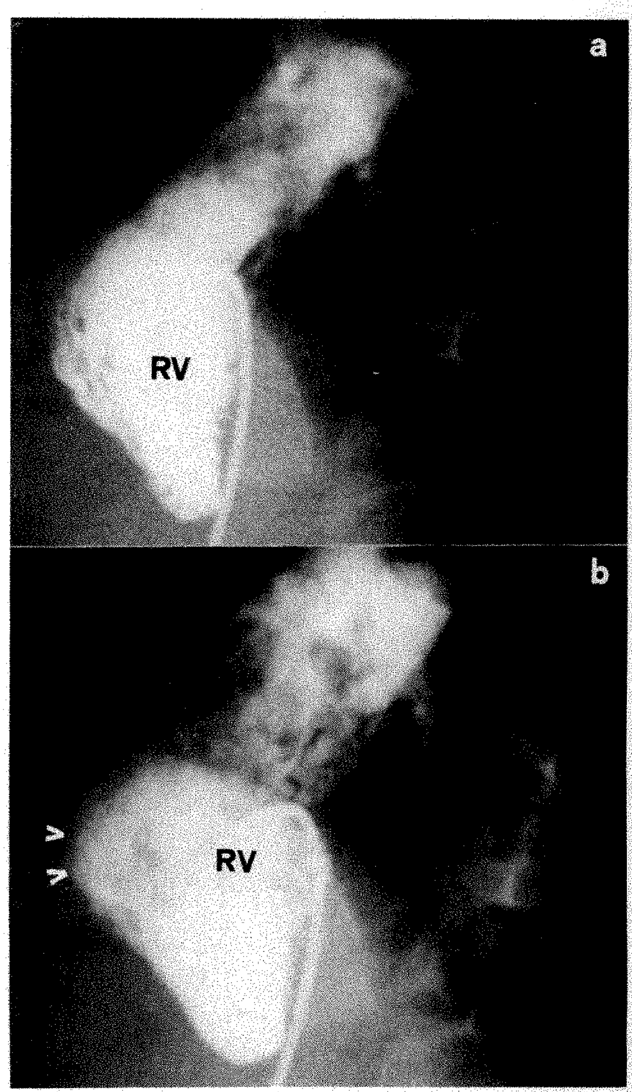

FIGURE 2. Angiocardiography of right ventricle (RV), end-systolic *(a)* and end-diastolic *(b)* left anterior oblique (long-axis) view: diastolic bulging of infundibular anterior wall *(arrow)*.

myopathy ($p < 0.0001$) but has a low sensitivity (56%). Bulgings of the infundibular anterior wall (Figure 2) and subtricuspid region (Figure 3) were the only other independently significant variables ($p = 0.004$ and $p = 0.002$, respectively) (Table III). Coexistence of these signs was associated with 96% specificity and 87.5% sensitivity.

DISCUSSION

Previous studies have defined the clinical characteristics of individuals with arrhythmogenic RV cardiomyopathy, with particular reference to arrhythmogenicity, repolarization alterations, familial clustering and the risk of sudden death.[8-14] It was stressed that echocardiography[15,16] and angiography[1-4,17] could constitute valid diagnostic tools. In the absence of diagnostic validation by means of endomyocardial biopsy, the specificity of the angiographic signs must be defined by comparison with normal subjects or patients with other diseases of the RV.

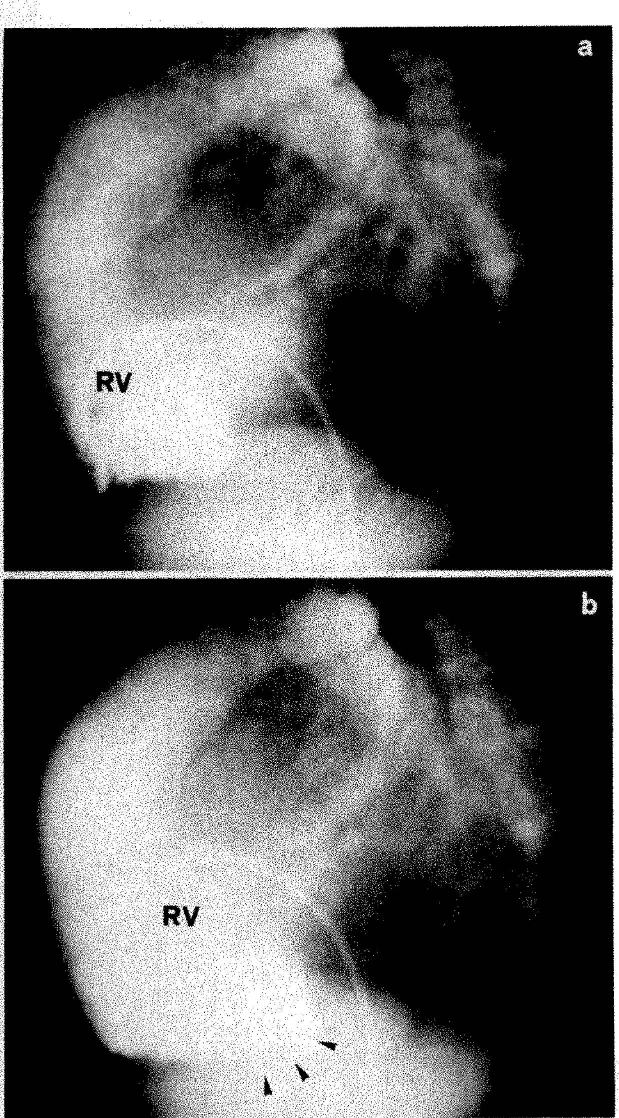

FIGURE 3. Angiocardiography of right ventricle (RV), end-systolic *(a)* and end-diastolic *(b)* anterolateral view: diastolic bulging of the subtricuspid region *(arrows)*.

TABLE III Logistic Discriminant Analysis

	Coefficient	SE	p Value
Transverse hypertrophy plus deep fissures	11.7	—	<0.0001
Bulging, infundibular anterior wall	3.1	0.9	0.004
Bulging, subtricuspid region	3.5	1.2	0.002

All other variables not significant at the 0.05 level

Sensitivity	87.5%
Specificity	95.9%
Correct	93.3%
False positive	9.7%
False negative	5.4%

SE = standard error.

These nosographic categories were determined with confidence by means of clinical, invasive and noninvasive examinations and definitely corroborated by endomyocardial biopsy. In this respect, a previous comparative study of biopsies from patients with arrhythmogenic RV cardiomyopathy, biventricular dilated cardiomyopathy and donor hearts (operative biopsy) showed that fatty substitution was the most distinctive histologic feature of arrhythmogenic RV cardiomyopathy.[18] The choice of biventricular dilated cardiomyopathy was dictated by the simple consideration that this disease also affects the RV. The atrial septal defect was chosen because it causes a volume overload without primary myocardial disease; in this manner, we could establish the extent to which the observed morphologic alterations were due to a primary myocardial disease or the consequence of a mere hemodynamic modification. Moreover, we could comparatively evaluate contractile performances and volumes under different conditions.

Our results show that arrhythmogenic RV cardiomyopathy, despite myocardial atrophy, has lower RV end-diastolic volumes than biventricular dilated cardiomyopathy and atrial septal defect itself. The mean ejection fraction was moderately depressed as in atrial septal defect, when compared to the severe depression in biventricular dilated cardiomyopathy. The left ventricle end-diastolic volume was slightly increased as compared to atrial septal defect and normal patients. In this respect, biventricular dilated cardiomyopathy showed the largest mean end-diastolic volume increase and most severe ejection fraction impairment.

These volumetric and hemodynamic findings confirm that a critical pump deficit in arrhythmogenic RV cardiomyopathy is not present in the right or in the left ventricle. Although the myocardial pathology is atrophic-regressive in nature, it does not markedly influence ventricular contractile performance, at least initially, but selectively alters the electrical stability of the ordinary myocardium. This would explain the common paradox of individuals who are capable of excellent cardiovascular performances in terms of cardiac output, but experience cardiac arrest and sudden death, with autopsy findings of arrhythmogenic RV cardiomyopathy.[14,19]

Qualitative wall structure analysis disclosed that simple transverse trabecular arrangement is not a parameter that may be used for diagnosis. Not only was this feature present in the group of normal subjects, but its frequency tends to increase as the chamber volume increases. On the other hand, trabecular thickness shows a similar behavior because hypertrophic trabeculae were observed in all the groups presenting dilated chambers.

Thickened and disarranged trabeculae give the wall margins a mammillated aspect, especially in the apex region, and this was observed in all the groups considered, regardless of the underlying cause. However, the association of hypertrophy, transverse arrangement and presence of deep conical images of fissures takes on particular importance. This association was found only in the arrhythmogenic RV cardiomyopathy group and is specific for this diagnosis, but has a low sensitivity.

Segmental analysis of RV contraction showed that the apex and the diaphragmatic wall were the portions mostly affected in arrhythmogenic RV cardiomyopathy, while the remaining RV free wall was usually spared. However, our analysis indicates that these segmental anomalies are not specific for the disease.

Of major significance instead is the deformation of the margins in 2 focal regions, such as the infundibular anterior wall and the subtricuspid area which, together with the apex, define the triangle of arrhythmogenic RV cardiomyopathy.[8] The presence of end-diastolic bulging in these 2 zones is significantly and independently related to the diagnostic definition of arrhythmogenic RV cardiomyopathy and increases sensitivity to 87.5%. These alterations are also present in the so-called "concealed form" and do not necessarily imply overt systo-diastolic abnormalities of the margins.[20,21]

Although some increases in the mean diastolic volumes and a slightly decreased ejection fraction were observed, the left ventricle did not present specific quantitative or qualitative findings enabling the diagnosis of arrhythmogenic RV cardiomyopathy. In fact, frankly, pathologic values were found only in the biventricular dilated cardiomyopathy group.

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Effect of Preload Change on Resting and Exercise Cardiac Performance in Hypertrophic Cardiomyopathy

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The purpose of this study was to investigate the hemodynamic responses, at rest and on exercise, of patients with hypertrophic cardiomyopathy to changes in circulating volume. After Swan-Ganz and radial arterial cannulation, 13 patients with hypertrophic cardiomyopathy performed maximal exercise tests after diuretic (frusemide 20 mg intravenously) and after fluid loading (0.9% saline at 10 ml/kg body weight intravenously) on different days. At rest, right atrial and pulmonary capillary wedge pressures increased with volume loading and decreased with a diuretic. There were no significant changes in the resting, supine cardiac or stroke indexes but in the upright position, the cardiac index and stroke index were higher after volume loading (2.5 ± 0.7 vs 2.2 ± 0.5 liters/min/m^2, $p < 0.05$; 33 ± 11 vs 27 ± 9 ml/m^2, $p < 0.005$, respectively). Although the right atrial, pulmonary arterial and pulmonary capillary wedge pressures were higher during exercise after volume loading, there were no significant differences in exercise heart rate, systemic blood pressure, cardiac index, stroke index, systemic vascular resistance index or overall exercise capacity compared to exercise after diuresis.

The data show that the cardiac index and stroke index, at supine rest and during upright exercise, were not influenced by the preload changes induced in these patients with hypertrophic cardiomyopathy. The results suggest that these patients are operating on the plateau of left ventricular Frank-Starling function (filling pressure/output) curve.

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The characteristic features of the left ventricle in hypertrophic cardiomyopathy are myocardial hypertrophy and a decreased cavity size often in association with diastolic dysfunction and/or an outflow tract gradient.[1] The cardiac filling pressure or preload is an important determinant of the performance of such ventricles at rest and on exercise. However, the effects of change in preload on haemodynamic function in hypertrophic cardiomyopathy have only been studied to a limited extent. The effects of large changes in blood volume[2] and the effects of vasodilator agents, such as amyl nitrite,[3] have been examined at cardiac catheterization with emphasis on the resultant changes in outflow tract gradient. However, there is no information on the hemodynamic consequences of modest changes in fluid volume such as those that might occur in clinical practice, for example, diuresis, dehydration or intravenous fluid administration. Such changes, diuresis in particular, might cause hemodynamic instability, especially on exercise when filling time is decreased. Therefore the purpose of this study was to investigate the resting and exercise hemodynamic response to variations in circulating volume, induced alternately by diuresis and fluid loading in patients with hypertrophic cardiomyopathy.

METHODS

Patients: The primary inclusion criterion for this study was the presence of exercise-limiting symptoms in patients with hypertrophic cardiomyopathy. The diagnosis of hypertrophic cardiomyopathy was based on the presence of typical clinical and electrocardiographic findings in association with a hypertrophied, nondilated left ventricle on 2-dimensional echocardiography in the absence of hypertension, valvular disease or any other systemic cause of ventricular hypertrophy.[4,5] Hypertrophic cardiomyopathy patients were not considered for study if the patient had any of the following: age <18 or >70 years; overt heart failure; uncontrolled arrhythmia or permanent pacemaker; history of myectomy or other cardiac surgery; history of coronary artery disease or myocardial infarction; or other major organ diseases. The first 13 patients who were suitable for study and willing to participate were enrolled. The clinical, echocardiographic and hemodynamic features of the 13 patients studied are listed in Table I. Two-dimensional and Doppler echocardiography were performed during admission for this study. Systolic anterior motion of the mitral valve associated with a Doppler-derived left ven-

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tricular outflow tract gradient >30 mm Hg was present in 7 patients and these were considered "obstructive." All medications were stopped 48 hours before the study. For symptomatic control of atrial fibrillation, 1 patient continued digoxin and 2 patients were receiving amiodarone.

Study protocol: The study protocol was approved by the hospital ethics committee. All patients gave written, informed consent. Patients were studied after an overnight fast. On the first day of investigation, a 7Fr, balloon-tipped, thermodilution, Swan-Ganz catheter was introduced under local anesthesia into the right pulmonary artery via the right internal jugular vein using fluoroscopic control. In 9 patients, the left radial artery was cannulated with a 20-gauge plastic cannula, while in 4 patients, systemic blood pressure was obtained by sphygmomanometer. After instrumentation, patients were taken to the exercise laboratory and sufficient time was allowed for recovery. Each patient then proceeded to perform an exercise test on consecutive days after either diuretic or volume loading. In the diuretic test, each patient was given 20 mg of frusemide intravenously and the exercise test commenced 2 hours later. In the volume loading test, each patient received 10 ml/kg of 0.9% saline solution intravenously over 30 minutes and the exercise test was performed immediately after completion of the infusion. The order of administration of diuretic or volume loading was randomized.

Exercise test: Maximum, symptom-limited exercise tests were performed on a bicycle ergometer (Bosch ERG 551) in the upright position. Before the investigation, patients performed pilot exercise tests to determine the work load at which each could exercise for ≥6 minutes without exhaustion. The definitive exercise tests were commenced at the predetermined work load (mean 28 W) and the work load was increased stepwise (mean 22 W) every 3 minutes until limited by symptoms.

Hemodynamic measurements: Pressures were measured with the P23 XL Spectramed transducer from a reference point 5 cm below the level of the angle of Louis in the supine position and from the fourth intercostal space at the sternal border in the upright position. Pressures were measured over ≥2 respiratory cycles and the mean pressures were obtained electronically. All the intravascular pressures were recorded using a polygraph recorder (Mingograf 7, Siemens) at a paper speed of 25 mm/s. Cardiac output was determined by the thermodilution technique using a cardiac output computer (Hemopro 1, Spectramed). At rest, the mean of 3 measurements that did not deviate by >10% from each other was taken. During exercise, the cardiac output was measured during the second and third minute of each stage and the mean of these 2 measurements was taken. Stroke index was calculated as cardiac index divided by the heart rate; the systemic vascular resistance index was considered to be the difference of mean blood pressure and mean right atrial pressure divided by the cardiac output and multiplied by body surface area. Before fluid manipulations, baseline measurements of heart

TABLE I Clinical, Echocardiographic and Hemodynamic Features of 13 Patients Studied

			Clinical Features			Doppler Echocardiographic Measurements					Hemodynamic Data			
Case No.	Age (yrs) & Sex	ECG Rhythm	Usual Symptoms	NYHA Class	Drug Therapy Before Study (daily doses in mg)	Pattern of LVH	IVS (mm)	LVEDD (mm)	LVESD (mm)	LVOT Gradient (mm Hg)	LVEDP* (mm Hg)	PCWP (mm Hg)	CI (liters/min/m^2)	SI (ml/m^2)
1	24/M	AF	DOE, palps	III	Amio 200, propranolol 40, warf	ASH	32	34	19	44	—	19	2	23
2	19/M	SR	Angina, presyncope	II	Nil	ASH	30	43	25	<20	—	11	2.6	36
3	47/F	SR	Angina, syncope	II	Amio 200	ASH	20	35	17	56	25	18	2.3	36
4	37/F	SR	Angina, presyncope	III	Propranolol 320	ASH	30	30	15	55	12	14	3.7	70
5	55/M	AF	DOE, syncope	III	Digoxin 0.125, frus 40, amil 5, warf	ASH	17	44	32	<20	10	14	1.9	24
6	57/F	SR	Fatigue, syncope	I	Nil	CONC	14	34	17	<20	14	12	2.8	40
7	42/M	SR	Angina, syncope	II	Atenolol 100	ASH	15	47	31	79	18	18	2.5	36
8	43/M	AF	DOE	III	Verapamil 240, hct. 50, amil 5, warf	ASH	15	49	33	<20	12	15	2	22
9	22/M	SR	DOE, palp	I	Atenolol 50	ASH	24	35	15	<20	—	11	3.6	49
10	37/M	SR	Angina	I	Verapamil 240	Apical	15	48	32	<20	15	9	2.8	38
11	68/F	SR	DOE	III	Diltiazem 360, frus 40, amil 5	ASH	27	42	23	110	24	27	3.2	42
12	43/F	SR	Fatigue, syncope	II	Disopyramide 200	ASH	21	37	23	36	—	6	2.3	27
13	50/M	SR	Angina, syncope	III	Nil	ASH	18	35	15	79	14	10	2.3	37
Mean ± SD	42 ± 14			2.2 ± 0.8			21 ± 7	40 ± 6	23 ± 7			14 ± 5	2.6 ± 0.6	37 ± 13

* LVEDP = (left ventricular end-diastolic pressure) obtained at routine cardiac catheterization within 3 years of study.
AF = atrial fibrillation; amil = amiloride; amio = amiodarone; ASH = asymmetric septal hypertrophy; CI = cardiac index; CONC = concentric hypertrophy; DOE = dyspnea on exertion; frus = frusemide; hct = hydrochlorothiazide; IVS = interventricular septum; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVOT = left ventricular outflow tract; NYHA = New York Heart Association class of symptoms; palps = palpitation; PCWP = mean pulmonary capillary wedge pressure; PW = posterior wall; SR = sinus rhythm; SI = stroke index; warf = warfarin.

rate, right atrial, pulmonary arterial, pulmonary capillary wedge, systemic arterial pressures and cardiac output were obtained in the supine position. Two hours after diuretic administration and immediately after volume loading, hemodynamic measurements were repeated in the supine and upright position at rest. Exercise was then begun in the upright position and hemodynamic measurements were made during each minute of exercise. For the purpose of analysis, maximum exercise was taken to be the highest 3-minute stage that was completed in both tests. Pressure measurements given for peak exercise are the values obtained in the third minute of this highest stage. Cardiac output measurements given for peak exercise are the mean of values obtained in the second and third minute of this stage.

Statistical analysis: All group data are expressed as the mean ± standard deviation. Data were analyzed by the 2-tailed Student's *t* test for paired and unpaired data as appropriate. A p value <0.05 was considered statistically significant.

RESULTS

The resting and exercise hemodynamic studies were completed without complication. The mean urine output after diuresis was 862 ± 259 ml and the mean saline load was 670 ± 132 ml.

Supine rest: Baseline measurements showed that the patients tended to have low stroke and cardiac indexes and high pulmonary capillary wedge pressures compared to reported normal values (Table II and Figure 1).[6] There were no significant differences between baseline data obtained before diuretic or before volume loading (Table II). The diuresis caused a decrease of 3 ± 3 mm Hg in right atrial pressure and 4 ± 3 mm Hg in mean pulmonary capillary wedge pressure with a concomitant decrease in systemic arterial pressure (Figure 1, A and C). Fluid loading increased the right atrial and pulmonary capillary wedge pressures by 4 ± 2 and 6 ± 3 mm Hg, respectively (Figure 1A) with a concomitant increase in pulmonary arterial pressure. These changes resulted in significant differences between pulmonary and systemic arterial pressures in the postdiuretic and postvolume load states (Table II). However the changes in filling pressures did not significantly alter heart rate, cardiac index or stroke index in the supine position.

Upright rest: Change of posture from the supine to the upright position caused significant decreases in right atrial, pulmonary arterial and pulmonary capillary wedge pressures, cardiac index and stroke index and increases in heart rate and systemic vascular resistance index in both the diuresed and volume loaded states (Table II). The differences in filling pressures and arterial pressures, between the diuresed- and volume-loaded states in the supine position were maintained in the upright position (Figures 2, A and C). However, in contrast to the supine position, the upright cardiac index and stroke index were significantly lower after diuresis compared to fluid loading (2.2 ± 0.5 vs 2.5 ± 0.7 liters/min/m^2 and 27 ± 9 vs 33 ± 11 ml/m^2, respectively).

TABLE II Effects of Diuretic and Volume Loading on Resting and Exercise Hemodynamics

	Baseline (supine)			Supine			Upright			Peak Exercise			Other Comparisons—p Values			
	Before Diuretic (DB)	Before Fluid (FB)	p Value	Diuretic (DS)	Fluid (FS)	p Value	Diuretic (DU)	Fluid (FU)	p Value	Diuretic (DE)	Fluid (FE)	p Value	DB vs DS	FB vs FS	DS vs DU	FS vs FU
HR (beats/min)	75 ± 14	74 ± 12	NS	76 ± 12	73 ± 13	NS	86 ± 15	79 ± 13	NS	132 ± 19	128 ± 22	NS	NS	NS	<0.01	<0.01
CI (liters/min/m^2)	2.7 ± 0.5	2.6 ± 0.6	NS	2.6 ± 0.5	2.8 ± 0.7	NS	2.2 ± 0.5	2.5 ± 0.7	<0.05	5.5 ± 2.4	5.3 ± 2.0	NS	NS	NS	<0.01	NS
SI (ml/m^2)	38 ± 11	38 ± 13	NS	36 ± 10	39 ± 13	NS	27 ± 9	33 ± 11	<0.005	42 ± 15	42 ± 13	NS	NS	NS	<0.01	<0.05
Mean RAP (mm Hg)	8 ± 3	6 ± 3	NS	5 ± 2	10 ± 3	<0.001	2 ± 2	7 ± 2	<0.001	6 ± 5	12 ± 4	<0.001	<0.05	<0.001	<0.01	<0.01
Mean PAP (mm Hg)	21 ± 5	22 ± 9	NS	19 ± 5	29 ± 15	<0.01	17 ± 4	21 ± 6	<0.001	30 ± 8	40 ± 11	<0.005	NS	<0.01	<0.05	<0.05
Mean PCWP (mm Hg)	15 ± 4	14 ± 6	NS	11 ± 4	20 ± 7	<0.001	8 ± 4	14 ± 5	<0.001	18 ± 8	27 ± 18	<0.005	<0.01	<0.001	<0.01	<0.01
SAP (mm Hg)	144 ± 22	135 ± 24	NS	130 ± 21	145 ± 36	<0.05	130 ± 28	145 ± 43	<0.05	161 ± 39	167 ± 60	NS	<0.05	NS	NS	NS
DAP (mm Hg)	79 ± 5	72 ± 5	NS	70 ± 6	74 ± 9	NS	75 ± 7	79 ± 11	NS	82 ± 8	87 ± 14	NS	<0.01	NS	<0.05	<0.05
SVRI (dynes s cm^5/m^2)	2,799 ± 436	2,732 ± 554	NS	2,683 ± 519	2,682 ± 674	NS	3,395 ± 659	3,148 ± 750	NS	1,717 ± 635	1,700 ± 640	NS	NS	NS	<0.01	<0.05

CI = cardiac index; DAP = diastolic arterial pressure; HR = heart rate; NS = not significant; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SAP = systolic arterial pressure; SI = stroke index; SVRI = systemic vascular resistance index.

No patient experienced symptoms of postural hypotension despite the lower pressures and cardiac output in the upright position.

Exercise tests: Exercise duration after diuretic (499 ± 145 seconds) was not significantly different from that after volume loading (466 ± 109 seconds, Figure 3) and the work loads achieved in both tests were similar (85 ± 61 watts after diuretic versus 83 ± 59 W after fluid). The exercise data showed the wide range of exercise performance that was to be expected from this group of patients with differing functional capacities (Figure 2B). The right atrial, pulmonary arterial and pulmonary capillary wedge pressures were significantly higher at peak exercise in the volume-loaded state compared to the diuresed state (Table II). However, there were no significant differences between exercise cardiac index or exercise stroke index in the 2 tests (5.3 ± 2.0 vs 5.5 ± 2.4 liters/min/m^2 and 42 ± 13 vs 42 ± 15 ml/m^2, respectively). It is noteworthy that the exercise stroke index was not significantly different from the baseline stroke index obtained in the supine position. Although there was no significant difference in exercise arterial pressures between diuretic and volume loading, the systolic pressure decreased in 2 patients and showed no increase in 1 patient after volume loading (Figure 2C). The 2 patients whose blood pressure decreased during exercise had mean pulmonary capillary wedge pressures at peak exercise of 40 and 28 mm Hg, respectively.

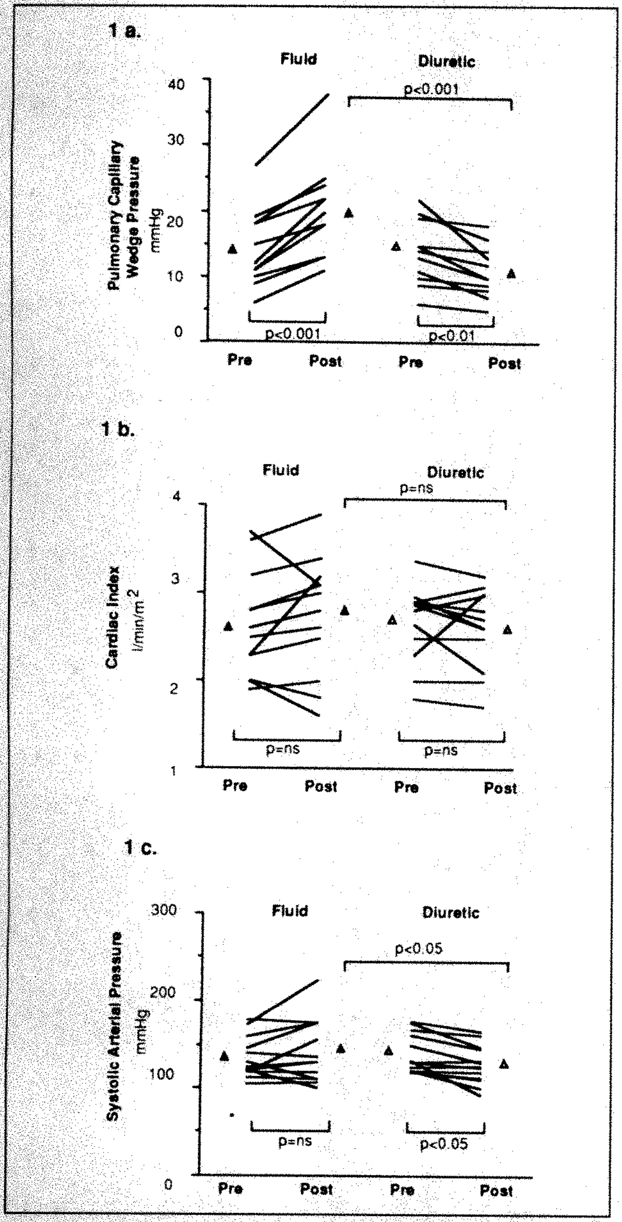

FIGURE 1. Hemodynamic measurements at rest in supine position before and after both diuresis and fluid loading. *a.*, pulmonary capillary wedge pressure; *b.*, cardiac index; *c.*, systolic arterial pressure.

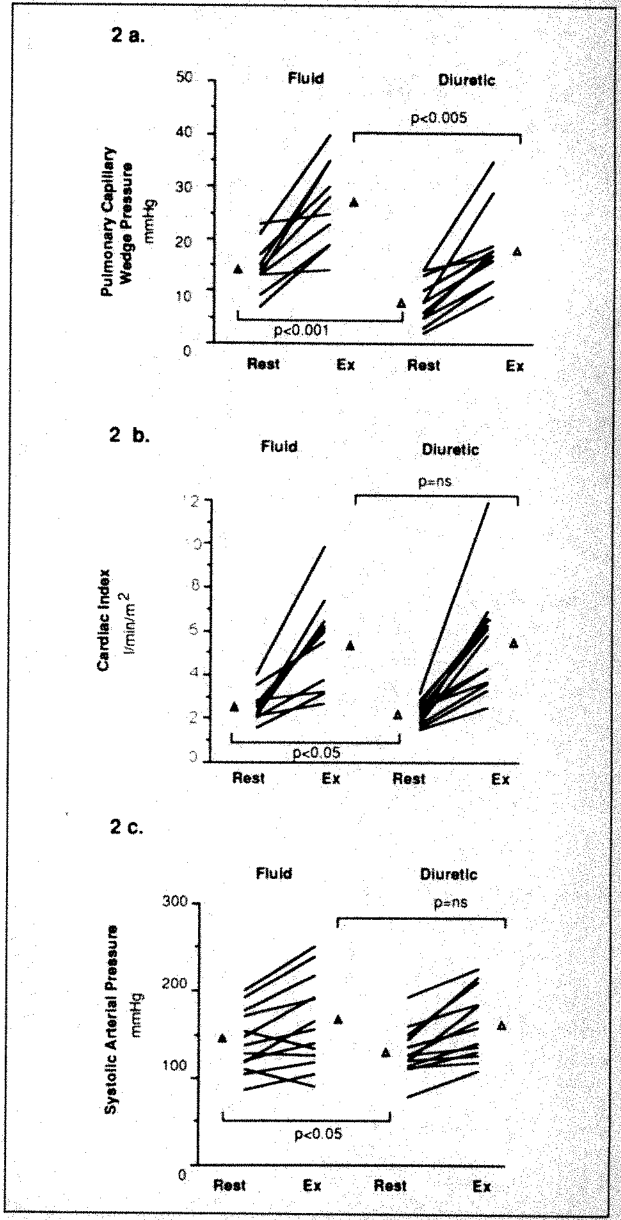

FIGURE 2. Hemodynamic measurements in the upright position at rest and at peak exercise after both diuresis and fluid loading. *a.*, pulmonary capillary wedge pressure; *b.*, cardiac index; *c.*, systolic arterial pressure.

Outflow tract gradient: In a subset analysis (data not shown), we compared the hemodynamic changes in patients with (n = 7) and without (n = 6) a left ventricular outflow tract gradient. There were no significant differences between these 2 groups in the hemodynamic responses to diuretic or to volume load.

DISCUSSION

The results of our study indicate that in this group of patients with hypertrophic cardiomyopathy: resting cardiac index and stroke index were not altered by significant changes in preload while supine, but were changed in the upright position; higher ventricular filling pressures during exercise after volume loading did not increase either stroke index, cardiac index or exercise capacity; and acute diuresis was well tolerated at rest and on exercise. Because of the invasive nature of this study, it was not possible to have a normal control group. However, comparison of our results to other published work on preload change suggests that the patients in our study behaved abnormally.[7-14]

Preload and resting hemodynamics: The Frank-Starling curve describes the relation between end-diastolic fiber length and contraction. Animal and human studies have attempted to define a corresponding relation between ventricular filling and stroke output in the intact organism under various conditions. The effect of acute increase of preload by rapid volume loading in dogs and baboons showed that stroke volume increased in association with an increase of left ventricular end-diastolic volume and pressures.[7,8] In normal subjects and in patients with coronary artery disease, it was found that acute blood volume expansion produced an increase of central venous, pulmonary capillary wedge and left ventricular end-diastolic pressures as well as cardiac output and stroke volume.[9-13] On the other hand, decrease of systemic venous return decreased the left ventricular end-diastolic pressure and volume and was accompanied by a decrease of cardiac output and stroke volume.[14-16] The results of our study in patients with hypertrophic cardiomyopathy are in agreement with previous investigators[17-19] that in the upright position, the resting cardiac index and stroke index are proportionately related to left ventricular filling. However, we found that a filling pressure/stroke output relation could not be shown in our patients in the supine position.

Preload and exercise hemodynamics: The findings of our study are in accordance with previous reports[17-22] that right atrial, pulmonary capillary wedge, systemic arterial pressures, cardiac index and stroke index all increase while the systemic vascular resistance decreases during exercise. There are few studies concerning the effect of blood volume change on cardiac performance during exercise, but recent studies in normal subjects have shown that blood volume expansion increases exercise cardiac output and stroke volume by 10 to 20%.[10,23-25] When the blood volume was decreased by 10% with a diuretic, the exercise cardiac output and stroke volume were decreased significantly.[24] The results of our study are different. We found that in patients with hypertrophic cardiomyopathy, the exercise cardiac index and stroke index were not influenced by the preload changes induced.

Preload/stroke output relation: There may be a number of reasons why we did not observe changes in cardiac output and stroke volume either at supine rest or on exercise after preload changes. Reflex adjustment to change in circulating volume involves complex mechanisms. Hypervolemia may result in reflex venodilatation and depression of myocardial contractility.[26] Hypovolemia may be compensated for by increase in heart rate and redistribution of blood flow. During exercise, adequate systemic venous return can be maintained by redistribution of blood flow and increase of venous tone in the exercising muscles.[27] Mechanisms that simply attenuated the effect of volume change on systemic venous return were taken into account in our study as cardiac filling pressures were measured directly, but changes in afterload and/or contractility could have

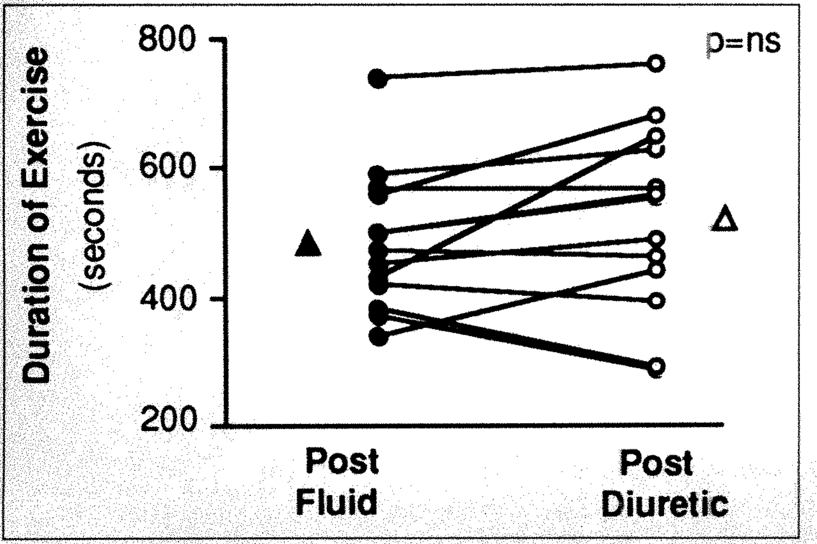

FIGURE 3. Duration of exercise after fluid loading and after diuretic. ns = not significant.

masked the presence of a filling pressure/output relation. Also, a vasodilatory action of frusemide could have confounded its diuretic effect.

The insensitivity of stroke output to preload changes in this study suggests that these patients are operating on the flat portion of the left ventricular filling pressure/output curve during supine rest and upright exercise. Only in the upright position at rest, when venous pooling in the lower limbs lowered filling pressure further, was a relation demonstrable. The results suggest that the patients had a limited use of the Frank-Starling effect to modulate stroke output during exercise and that their pressure-volume curves were steep, that is, increases in ventricular filling pressure resulted in disproportionately greater increases in ventricular wall stress. The relation between ventricular filling pressure and volume in these patients could be adversely affected by any one of (or a combination of) the diastolic abnormalities described in hypertrophic cardiomyopathy, namely, impaired relaxation and filling,[28,29] increased muscle mass and stiffness[30,31] leading to decreased distensibility and a small cavity size[28,30] (as seen in our patients, Table I). It is possible that the Frank-Starling fiber length/contraction relation may be preserved but myocardial fibers may fail to stretch due to chamber stiffness in hypertrophic cardiomyopathy. Thus, the observed failure of stroke output to respond to large variations in preload may be explained by diastolic dysfunction, but in this study, it was not possible to assess the relative contributions of different diastolic abnormalities.

Clinical implications: Diuretics have generally been thought to be contraindicated in hypertrophic cardiomyopathy. However, no clinical study on the use of diuretics in hypertrophic cardiomyopathy has been previously reported. Our study shows that acute diuresis is well tolerated at rest and on exercise in a selected group of patients with hypertrophic cardiomyopathy. Although outflow tract gradients were not measured in this study, cardiac output and blood pressure were not compromised by diuresis, suggesting that there was no significant adverse effect on ventricular function. No hemodynamic benefit was obtained by exercising in the volume loaded state and indeed, systemic arterial pressure decreased in 2 patients during exercise. These results suggest that diuretics may be used safely in selected patients with hypertrophic cardiomyopathy to decrease left ventricular filling pressures and thereby potentially relieve symptoms. Further studies are needed to establish the precise role of diuretics in the medical management of hypertrophic cardiomyopathy.

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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. *Am J Cardiol* 1984;53:900–915.

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Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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Spontaneous Beat-to-Beat Variation of PR Interval in Normal Children

Richard L. Donnerstein, MD, William A. Scott, MD, and Thomas R. Lloyd, MD

Autonomic innervation of the heart both directly and indirectly influences conduction through the atrioventricular (AV) node.[1-3] Sympathetic stimulation directly decreases cycle length by way of the sinoatrial node and enhances AV conduction through the AV node. Parasympathetic activity directly increases cycle length and prolongs AV conduction. However, changes in cycle length cause opposite changes in AV conduction time (indirect effect), thereby modulating direct effects of autonomic activity on AV conduction.[1-3] This study noninvasively investigated the net influence of these opposing factors on AV conduction during spontaneous variation of cycle length.

After positioning electrodes to obtain P waves of maximum amplitude, continuous 250-second electrocardiograms were obtained from supine, resting, normal children. The output of an electrocardiographic monitor (Hewlett-Packard, model 78833B, Hewlett-Packard GMBH, West Germany) was high-pass filtered at 10 Hz to reduce low frequency baseline shifts and enhance detection of P waves. The output of the filter underwent a 12-bit analog-to-digital conversion (MacAdios II, GW Instruments, Cambridge, Massachusetts) at 2,000 Hz and digital data were transferred to a Macintosh IIcx computer (Apple Computer Inc., Cupertino, California) for signal processing. Separate templates of the P and R waves were formed by averaging data from 10 beats. Using a least-squared error analysis, individual P and R waves were aligned to their associated template to precisely define their locations with a resolution of 0.5 ms. PR and PP (cycle length) intervals were calculated and regression analysis was used to determine the relation between PR intervals and preceding PP intervals. The cycle preceding and the 7 cycles following any ectopic beats were excluded from analysis. Data from subjects with >5 ectopic beats were not included in the analysis.

Complete studies were obtained from 25 normal children, ages 0.5 to 16 years. Data from 4 children with intermittent junctional rhythm or frequent ectopic beats were excluded. An average of 344 beats (range 243 to 583) were analyzed from each subject. Individual mean heart rates ranged from 59 to 139 beats/min. Both cycle length and PR interval increased with age ($r = 0.63$ *and* 0.58*, respectively,* $p < 0.01$)*. Continuous data acquired over a 1-minute period from a 12-year-old girl are shown in Figure 1. Changes in cycle length (top panel) are associated with changes of opposite direction in PR interval (bottom panel). Figure 2 shows the relation between PR interval and cycle length for all measurements obtained from this subject. In this example the PR interval decreases with increasing PP interval with a slope of* -0.042 ($r = 0.82, p < 0.001$)*. PR interval varied significantly* ($p < 0.01$) *with cycle length in 17 of 21 children. The PR interval decreased with increasing cycle length in 14 of 17 subjects and increased in 3 of 17. In the other 4 children, the slope of the relation did not differ significantly from zero. As shown in Figure 3, the direction and magnitude of the regression slope between PR interval and cycle length correlated with the standard deviation of cycle length* ($r = 0.67$, $p < 0.001$)*.*

Using a noninvasive technique, we have demonstrated that (1) PR interval changes on a beat-to-beat basis in normal children, and (2) these changes depend on the magnitude of spontaneous cycle length variation. Previ-

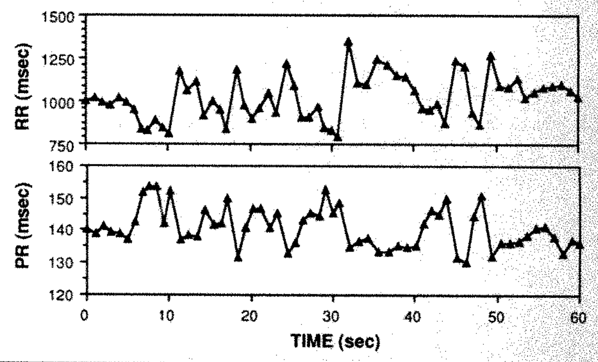

FIGURE 1. Continuous simultaneous measurements of cycle length *(upper panel)* and PR interval *(lower panel)* obtained from a 12-year-old subject. PR interval varies inversely with changes in cycle length. PP = cycle length; PR = PR interval.

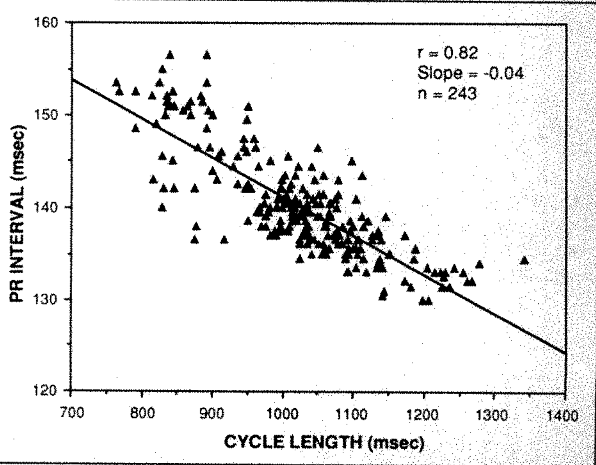

FIGURE 2. Relation between PR interval and cycle length obtained from the subject whose data are shown in Figure 1. Results of regression analysis are also shown.

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ous studies of PR interval have focused on mean values obtained from standard electrocardiograms (ECGs) rather than accurate beat-to-beat measurements. Group mean data obtained from normal children in the former manner showed that mean PR interval lengthens with increased mean cycle length (decreased heart rate).[4] In our subjects, mean cycle length and mean PR interval increased an average of 22 and 2.5 ms/year respectively, similar to values obtained in larger populations.[4] Cycle-to-cycle variations of both cycle length and PR interval were unrelated to subject age in our population, consistent with intracardiac studies of AV conduction.[5] As opposed to group mean results obtained from standard ECGs, our study demonstrated that beat-to-beat PR interval decreases with increasing cycle length in most normal children. However, this finding was not universal. When PP variation was small, PR interval and PP changed in similar directions; when PP variation was large, the inverse relation was noted.

Whereas assessment of heart rate variation is frequently used as a measure of autonomic function, beat-to-beat changes in AV conduction have not been comprehensively studied in humans. Assessment of changes in PR interval requires precise location of both P and R waves of the electrocardiogram. We noninvasively located the P and R waves with a high degree of temporal resolution (0.5 ms) using a combination of analog filtering and digital signal-processing techniques. It is unlikely that our results were significantly affected by atrial ectopy. All ECGs were reviewed and ectopic beats were excluded from analysis. Moreover, the inverse relation between PR interval and cycle length held continuously over a wide range of cycle lengths (Figure 2). PR interval depended on cycle length variation in children of similar ages and respiratory rates and, therefore, it is doubtful that our results were significantly influenced by respiratory effects on P-wave morphology. Although changes in PR interval generally reflect changes in AV conduction time, we cannot eliminate the possibility that our measurements of PR interval were influenced by minor shifts in pacemaker site, atrial activation sequence or atrial conduction velocities.[1]

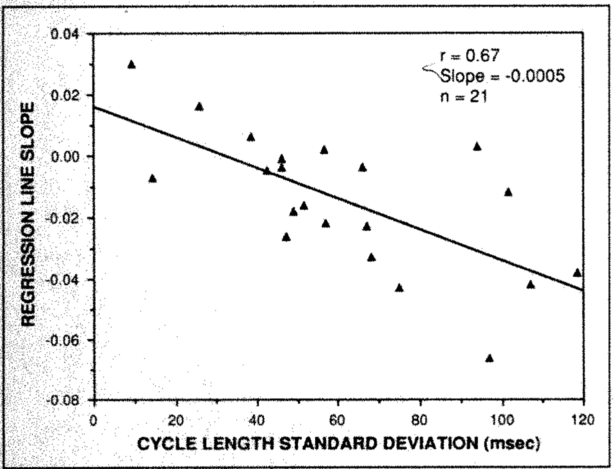

FIGURE 3. Relation between slope of regression line (PR interval versus cycle length) and standard deviation of cycle length. All analyzed data are included. Results of regression analysis are also shown.

Heart rate variation is primarily modulated by parasympathetic nervous system activity.[6] Increasing parasympathetic tone results in greater heart rate variation and, as our beat-to-beat data suggest, more negative correlation between cycle length and PR interval. Multiple factors may influence the interaction between cycle length and PR interval including relative responses of the sinus and AV nodes to autonomic innervation, effects of cycle length on AV nodal conduction, and changes in atrial conduction. Martin[1] demonstrated shortening of AV conduction time associated with increased cycle length in response to isolated vagal stimuli in a canine model. However, previous intracardiac studies of the spontaneous beat-to-beat variation of AV conduction in dogs have shown parallel changes in AV conduction time and cycle length.[2,3] Using high resolution digital signal processing, we have found that PR interval varies inversely with cycle length in most children. These contrasting results may be due to differences in technique, species or maturity, and highlight a complex interaction of direct and indirect effects of the autonomic nervous system on atrial and AV nodal conduction.[1-3] Noninvasive quantification of the beat-to-beat relation between PR interval and cycle length may represent a new means of assessing the influence of autonomic innervation on the cardiac conduction system.

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Atrial Flutter in Patients Treated for Atrial Fibrillation with Propafenone

Challon J. Murdock, MBBS, Alison E. Kyles, John A. Yeung-Lai-Wah, MB, ChB, Anzhen Qi, MD, Shirley Vorderbrugge, BSN, and Charles R. Kerr, MD

The class IC antiarrhythmic drug, propafenone, has been used successfully for the prevention of atrial fibrillation (AF), with few reported adverse cardiovascular effects.[1-3] Propafenone depresses the rate of rise and amplitude of phase 0 of the action potential, slowing conduction in the atrium.[4] Although it has mild β-adrenergic antagonist effects, it has relatively less effect on atrioventricular refractoriness, although in AF the ventricular response may slow.[5] With slower atrial arrhythmias such as atrial flutter, where less concealment of conduction occurs, it is possible that the same effect on ventricular rate may not be seen. This study defines the incidence of atrial flutter developing in a heterogeneous population of patients with recurrent AF and observes the ventricular response during this arrhythmia.

The case records of patients with a diagnosis of paroxysmal AF attending the Arrhythmia Service at University Hospital between January 1984 and December 1988 were examined. Therapy in 82 patients was begun with propafenone. In 13 of these patients (16%) atrial flutter as well as AF had been documented, 5 while taking digoxin alone, 4 while taking quinidine and digoxin, 1 while taking propranolol and 3 while taking no medications. Patients had undergone an average of 3.0 (range 0 to 7) drug trials unsuccessfully before entry into the study. The mean duration of follow-up was 30 months (range 3 to 58). AF was documented by 12-lead electrocardiogram or by Holter monitor in all patients. After commencing treatment, patients were seen at 3- to 6-month intervals or if significant symptoms occurred.

The 12-lead electrocardiograms of all patients were examined for the subsequent development of atrial flutter during propafenone therapy. In these patients, the ventricular rates during AF, both before any antiarrhythmic therapy as well as during the antiarrhythmic therapy at presentation to this hospital, were compared with the ventricular rate during atrial flutter with propafenone. In addition, changes in the PR intervals and QRS duration with propafenone administration were noted.

Results are expressed as mean ± 1 standard deviation. Comparison between the means was obtained using Student's t *test for unpaired data.*

Atrial flutter occurred in 14 patients during propafenone therapy. This was a new arrhythmia in 8 patients (9%). Atrial flutter recurred in 6 of the 13 patients who had this arrhythmia before the initiation of therapy. The time from commencing propafenone to the onset of atrial flutter in these 14 patients was 10 ± 14 months (range 2 days to 50 months). The atrial flutter rate during propafenone treatment was 246 ± 38 beats/min. In the 6 patients with atrial flutter before and during propafenone therapy the atrial rate slowed from 287 ± 17 to 258 ± 39 ms ($p < 0.05$) (Table I). The PR interval during sinus rhythm prolonged in all but 2 patients by >0.02 second (range 0.02 to 0.08). No patient developed higher degrees of atrioventricular block.

At presentation, before propafenone therapy, 12 of these 14 patients were receiving antiarrhythmic therapy for recurrent AF. This included digoxin alone (6 patients), β-blocking agents alone (3 patients), procainamide alone (1 patient), digoxin and quinidine (1 patient) and digoxin and propranolol (1 patient). The ventricular rate during AF recorded during propafenone therapy was 103 ± 27 beats/min. This was significantly less than the rate during atrial flutter with propafenone (139 ± 52 beats/min, $p < 0.03$). The ventricular response to AF before the initiation of any antiarrhythmic therapy could be determined in only 8 patients and was 151 ± 34

TABLE I Characteristics of Atrial Flutter Before and During Propafenone Therapy

Pt.	Drugs	A Rate (beats/min)	V Rate (beats/min)	Dose P (mg/day)	A Rate (beats/min)	V Rate (beats/min)
1	0	300	140	900	275	275
2	0	300	150	600	300	150
3	Quinidine Digoxin	260	130	900	240	120
4	Digoxin	285	142	900	215	85
5	Quinidine Digoxin	275	135	600	275	135
6	Propranolol	300	80	900	240	120
Mean ± SD		287 ± 17	130 ± 25		258 ± 39*	148 ± 66†

A = atrial; NS = not significant; P = propafenone; SD = standard deviation; V = ventricular.
* $p < 0.05$ compared with values before propafenone; † Difference not significant compared with values before propafenone.

From University Hospital (UBC Site), University of British Columbia, 2211 Westbrook Mall, Vancouver, B.C., Canada, V6T 2B5. Dr. Murdock is receiving the WA and MG Saw Medical Research Fellowship. This study was supported in part by grants from the Heart Foundation of British Columbia and the Chest, Heart and Stroke Association of Britain. Manuscript received June 20, 1989; revised manuscript received and accepted May 3, 1990.

beats/min. This was similar to the ventricular response during flutter of 146 ± 66 beats/min in the same patients after therapy with propafenone was begun (difference not significant).

The QRS complex duration prolonged from 0.10 ± 0.01 second during AF without propafenone to 0.12 ± 0.03 second during atrial flutter with propafenone therapy (p <0.02). New QRS complex prolongation to at least 0.14 ms developed in 4 patients during atrial flutter. Of these patients 2 had 1:1 atrioventricular (AV) conduction of atrial flutter at 200 (Figure 1) and 275 beats/min, respectively. The other 2 patients had 2:1 AV block with a ventricular response of 150 and 115 beats/min, respectively. A fifth patient developed 1:1 conduction of atrial flutter at a rate of 200 beats/min with a QRS width of 0.16 second after combining quinidine with propafenone. In the 3 patients with 1:1 AV conduction during tachycardia, increased AV block during tachycardia resulted in narrowing of the QRS complex (Figure 2).

This study demonstrates that atrial flutter may frequently develop in patients with recurrent AF who are being treated with propafenone. It also highlights the

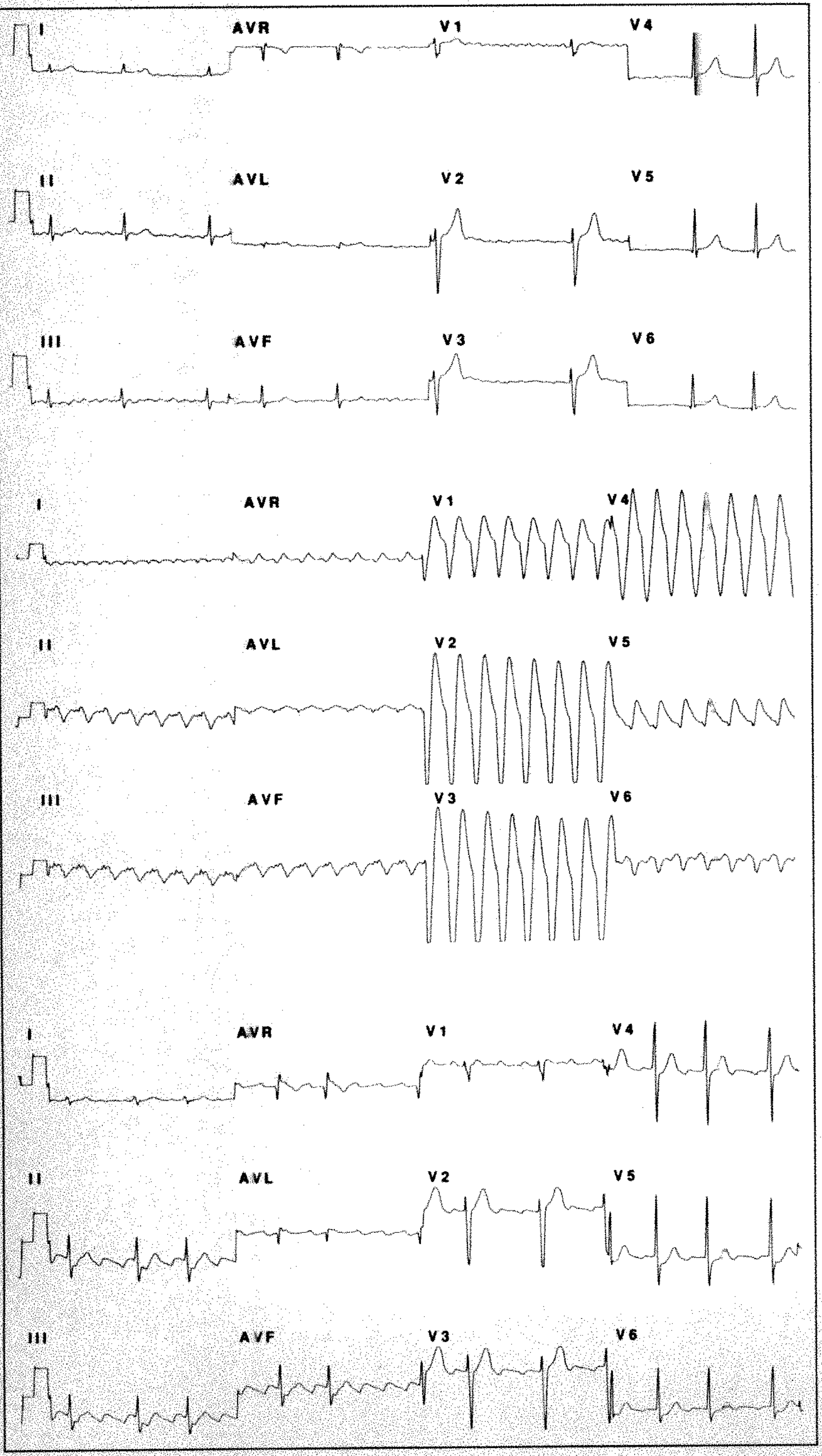

FIGURE 1. Twelve-lead electrocardiograms demonstrating development of wide-complex tachycardia. *Top,* electrocardiogram during atrial fibrillation before initiation of propafenone therapy; *middle,* wide QRS complex tachycardia due to atrial flutter with 1:1 atrioventricular conduction at a rate of 200 beats/min; *bottom,* after administration of verapamil, increase in atrioventricular block reveals slow atrial flutter at 200 beats/min with variable atrioventricular conduction and narrowing of the QRS complex.

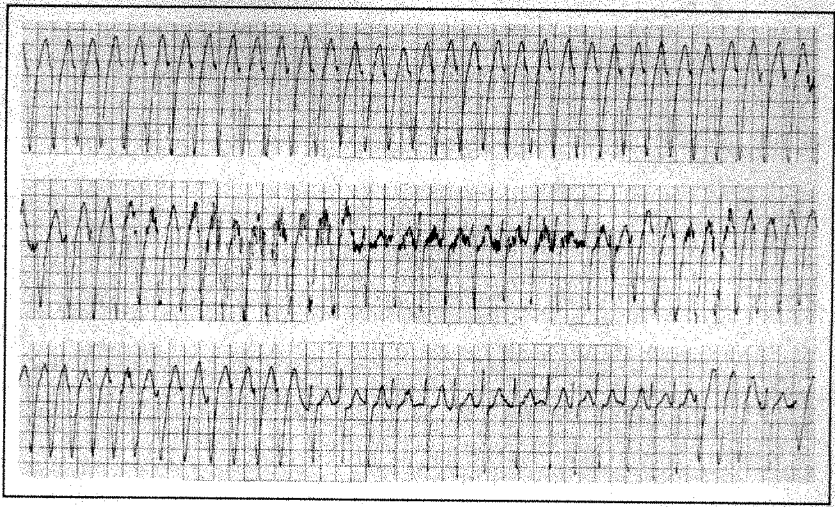

FIGURE 2. Continuous rhythm strip recorded at 25 mm/s demonstrating a wide-complex tachycardia at 200 beats/min due to 1:1 atrioventricular conduction of atrial flutter. An increase in the degree of atrioventricular block is associated with slowing and some irregularity of the ventricular response and narrowing of the QRS complexes.

potential for a rapid ventricular response should atrial flutter develop.

The atrial rate during atrial flutter with propafenone was relatively slow, yet the ventricular response was similar to that observed during AF in the unmedicated state, implying less concealed AV conduction during this slow atrial flutter. Propafenone has a β-adrenoreceptor antagonist effect, but this study suggests that this effect plus the direct effects of propafenone on AV nodal refractoriness are insufficient to prevent rapid AV conduction. A wide-complex tachycardia, which might be confused with ventricular tachycardia, was seen in 4 patients taking propafenone alone and in a fifth patient taking propafenone with quinidine. The development of the wide QRS complex during tachycardia was demonstrated to be rate-related in 3 of these patients, likely due to the use-dependent effects of propafenone on myocardial conduction. A similar complication has been reported with flecainide therapy, but not previously with propafenone.[6]

The development of atrial flutter, frequently at a slow rate, may arise owing to the electrophysiologic effects of the drug. Propafenone greatly slows atrial conduction with only a minor prolongation of refractoriness, favoring perpetuation of reentry with creation of a larger excitable gap, particularly if reentry developed around an anatomic obstacle. Atrial flutter might also start more easily because atrial premature beats would more readily develop the critical delay and unidirectional block necessary for the initiation of reentry.

Another possible explanation is that patients with AF are also prone to develop atrial flutter and that the association with propafenone therapy was coincidental. Atrial flutter may have occurred unrecognized in patients believed to have only AF. This was a retrospective study with no control group. The incidence of atrial flutter developing in patients receiving no treatment or taking other antiarrhythmic therapy is not known. The possibility that patients may have had unrecorded episodes of atrial flutter before propafenone administration cannot be excluded.

Because of the potential for transition of AF to atrial flutter with a rapid ventricular response, consideration should be given for the concomitant administration of drugs such as digoxin or β-adrenergic blockers that prolong AV nodal refractoriness.

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Transesophageal Echocardiography in the Evaluation of Prosthetic and Native Aortic Valves

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Transesophageal echocardiography (TEE) has gained relatively slow acceptance in North America despite its widespread popularity in Europe and Japan.[1,2] Through this new acoustic window high-quality images of certain posteriorly located cardiovascular structures such as the interatrial septum, the left atrial appendage and the thoracic aorta, which often prove difficult to evaluate in detail from the precordium, can be readily obtained. The improved miniaturization and sophistication of esophageal transducers, which incorporate simultaneous Doppler and color flow imaging, has precipitated application of the technique both in the intraoperative and outpatient setting. Transesophageal studies of dysfunctional native mitral valves have been found extremely helpful in defining the cause and quantifying the degree of regurgitation.[3] The advantage of TEE in assessing prosthetic mitral valves is even greater because the prosthetic material, which frequently attenuates the signal and masks the presence and extent of a regurgitant jet on surface echocardiography (echo),[4] is no longer a problem. The same advantage of TEE over surface echo has been described to a limited extent in native aortic valve disease,[5,6] but this has not been demonstrated in patients with prosthetic valves in whom signal quality from within the prosthesis is said to be poor and visualization of the leaflets incomplete.[7] These factors prompted us to review our initial experience with TEE in evaluating aortic valve dysfunction in both native and prosthetic valves.

Between August 1, 1988, and August 1, 1989, 127 TEE studies were performed at University of California San Diego Medical Center and at the San Diego Naval Hospital. Of these, 30 studies were performed specifically to assess aortic valve anatomy and function. These 30 patients comprise the current study population. All studies were performed using either a Hewlett-Packard Sonos 500 or Sonos 1000 Ultrasound System (Andover, Mass) incorporating a 5-MHz transesophageal transducer (model 21362A). All patients had standard 2-dimensional echocardiographic studies at our institutions utilizing a Hewlett-Packard Sonos 500 or 1000 with a 2.5- or 3.5-MHz transthoracic transducer. Of the valves studied, 11 were native aortic valves, 12 were tissue prostheses (11 porcine, 1 homograft), 4 were Bjork-Shiley mechanical prostheses, and 1 each a Medtronic-Hall prosthesis, a Starr-Edwards prosthesis and a St. Jude bileaflet prosthesis. All but 1 of the studies were performed in awake patients. Studies performed in awake patients involved the use of topical anesthetic spray. When necessary, 25 to 50 μg of the opiate fentanyl was given intravenously for sedation. All procedures were done with monitoring of pulse and blood pressure

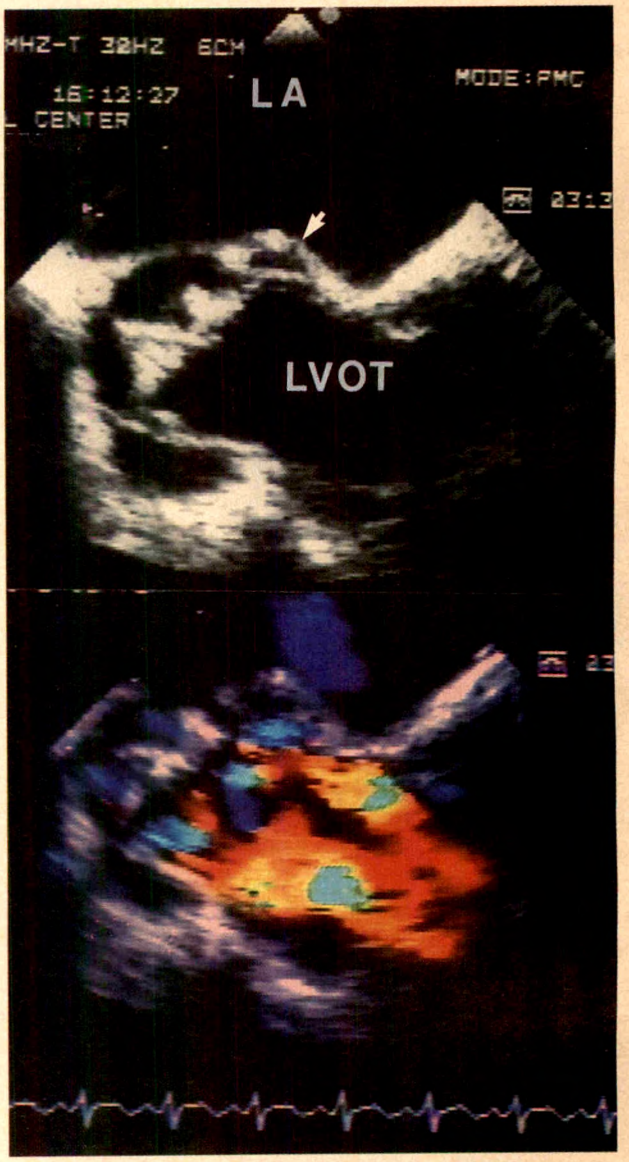

FIGURE 1. ***Top,*** **2-dimensional echocardiographic image of the left ventricular outflow tract (LVOT) and aortic valve with a bulky vegetation and an abscess cavity (*arrow*) between the aortic valve and the left atrium (LA) at the base of the mitral valve.** ***Bottom,*** **color flow image demonstrating the aortic insufficiency and flow within the abscess cavity.**

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The opinions stated herein are those of the authors and do not necessarily reflect the opinions or policies of the Department of the Navy or the Department of Defense.

and equipment for suctioning the airway and cardiopulmonary resuscitation was immediately available. In general, patients with prosthetic valves received antibiotic prophylaxis (1 million units of intravenous penicillin G) immediately before the procedure. One patient underwent imaging in the operating room immediately before cardiac surgery.

Routine TEE images included the left ventricular short-axis view from the gastric fundus and esophageal images demonstrating 4-chamber, left ventricular outflow tract, aortic root and basal views, with ultrasound depth varying from 4 to 16 cm depending on the focus of imaging.[3,8] *Images were recorded continuously using 2-dimensional echocardiography, color flow mapping and pulsed-wave Doppler and combined color flow/M-mode for timing of regurgitant jets. Typical studies in awake patients were 9 to 15 minutes in duration. All awake patient studies were well tolerated with no complications reported. Confirmation of the TEE findings was available in 18 of the cases from either surgery, catheterization or autopsy.*

TEE provided useful information in patients with native aortic valve disease. A 35-year-old woman was receiving treatment for enterococcal endocarditis and was continuing to have high, spiking fevers despite appropriate antibiotics. Surface echo had shown large bulky vegetations that appeared unchanged over 3 weeks. Figure 1 demonstrates a paravalvular abscess which was found at TEE. A color flow jet was demonstrated within the echolucent space. The patient underwent surgery without further diagnostic imaging with confirmation of the paravalvular abscess. A 27-year-old woman was considered by surface echo to have a subaortic membrane causing severe stenosis. TEE confirmed this membrane and also demonstrated filamentous communications between the membrane and 2 of the cusps of the aortic valve. This information was sufficient for surgical repair without the need for cardiac catheterization. Two patients, both receiving therapy for bacterial endocarditis, were studied and found to have severe aortic insufficiency on surface echo; in 1 patient an eccentric left atrial jet was also noted. At TEE, both patients were found to have a subvalvular abscess in the mitral-aortic intervalvular fibrosa with an obvious outflow tract to left atrial communication (Figure 2). Surgery was performed on both without preoperative cardiac catheterization where confirmation of the TEE findings was made. In addition, knowledge of the outflow tract to left atrial communication in these patients was useful to the cardiac surgeons in their surgical approach. The surface echo was adequate for identification of the valve pathology in only 4 of the 11 patients with native aortic valve disease. TEE was particularly helpful in identifying paravalvular disease not seen from surface echo.

Nineteen patients had prosthetic aortic valves (4 Bjork-Shiley, 12 tissue, 1 each St. Jude, Starr-Edwards and Medtronic Hall) varying in age from 4 days to 23 years. In only 2 of the prosthetic valves (1 porcine and 1 Bjork-Shiley) was visualization of the valve disc or leaflets suboptimal. In all other cases, the orientation of the valve was such that motion of the disc or leaflets could be evaluated adequately without significant attenuation by the surrounding prosthetic material. In 2 cases, an echodensity considered to represent thrombus or vegetation was seen either on the aortic side of the valve in systole or on the ventricular side of the valve in diastole (Figure 3), appearing from behind the attenuation produced by the prosthetic material. One patient was found to have limited opening of both discs of a St. Jude prosthesis (Figure 4), which was confirmed by both angiography and surgery. As with native valves, the greatest advantage of TEE involved the identification of paravalvular pathology. Seven patients were found to have paravalvular involvement including an aorta to left or right atrial communication in 3 and paravalvular aortic regurgitation in 4. In 1 of the 2 patients with an aorta to left atrial communication, the surface echo identified an unusual left atrial jet thought to be mitral regurgitation but proved to be the fistulous communication on TEE. No left atrial jet by surface echo was seen in the other patient. Although aortic insufficiency by color and spectral Doppler was found on surface echo in all 4 patients with paravalvular aortic regurgitation, only TEE was able to localize the site of regurgitation accurately.

This report describes our initial experiences with TEE in the evaluation of native and prosthetic aortic valve disease primarily in the awake patient. The procedure, whether performed in prosthetic or native valves, appears to be of diagnostic value in most patients. This is distinctly opposite to the experience of others[7] who pointed out the shortcomings of TEE in visualizing the leaflets of aortic tissue prosthetic valves. These investigators did, however, point out that the sewing ring of the prosthesis was well seen. A possible explanation for this discrepancy

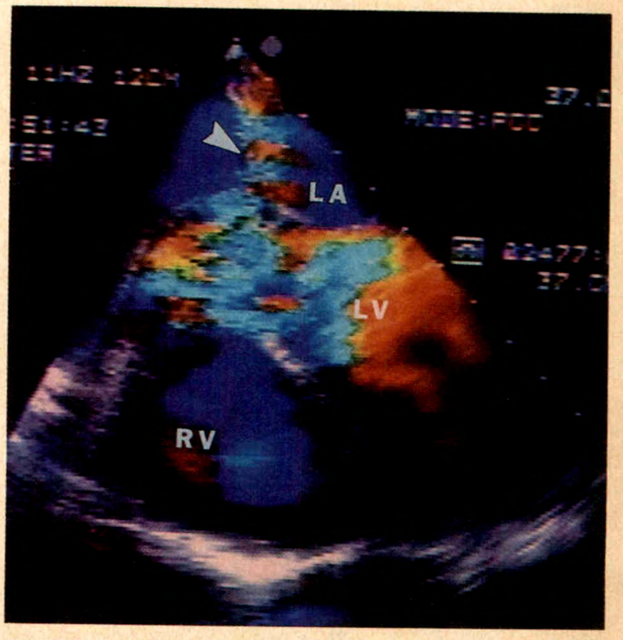

FIGURE 2. A left ventricular outflow tract view of a native aortic valve with a prominent systolic outflow tract to left atrial fistula (*arrow*). LA = left atrium; LV = left ventricle; RV = right ventricle.

in experiences with TEE in evaluating aortic valve anatomy and function lies in the site of the abnormalities detected in cases of acute valvular dysfunction either in native or prosthetic valves. The abnormality most often lies in and around the anulus or sewing ring, especially near the sinus of Valsalva of the noncoronary cusp or in the mitral-aortic intervalvular fibrosa,[9] with abscess, aneurysm, dehiscence or fistula, all of which are well seen on TEE. The clinical importance of identifying these abnormalities on TEE is well emphasized in our series because 6 patients with infective endocarditis were referred to surgery for valve replacement solely on the basis of para-

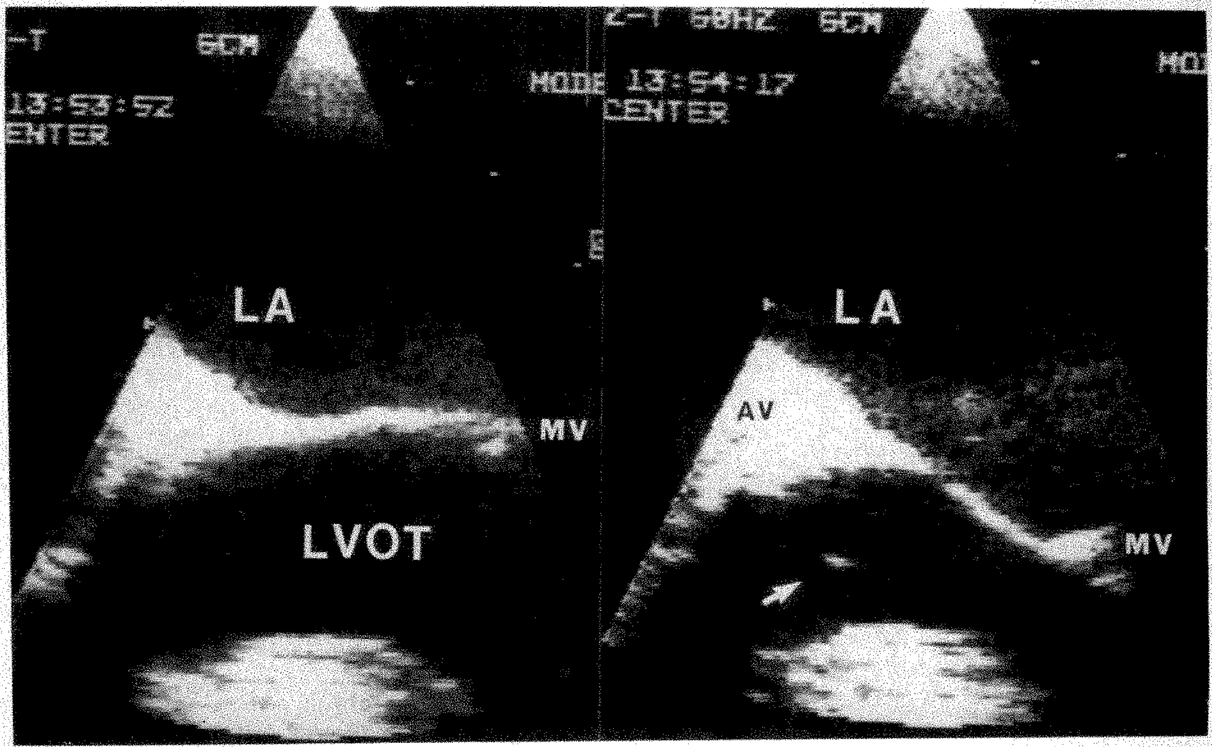

FIGURE 3. ***Left,*** **enlarged, off-axis view of the left atrium (LA) and left ventricular outflow tract (LVOT) in systole with no evidence for an echodensity in the LVOT. MV = anterior leaflet of the mitral valve.** ***Right,*** **similar view of LA and LVOT in diastole with an echodensity (*arrow*) that was confirmed to be thrombotic material adherent to the aortic valve disc at surgery. The aortic valve (AV) ring is only partially seen in this view.**

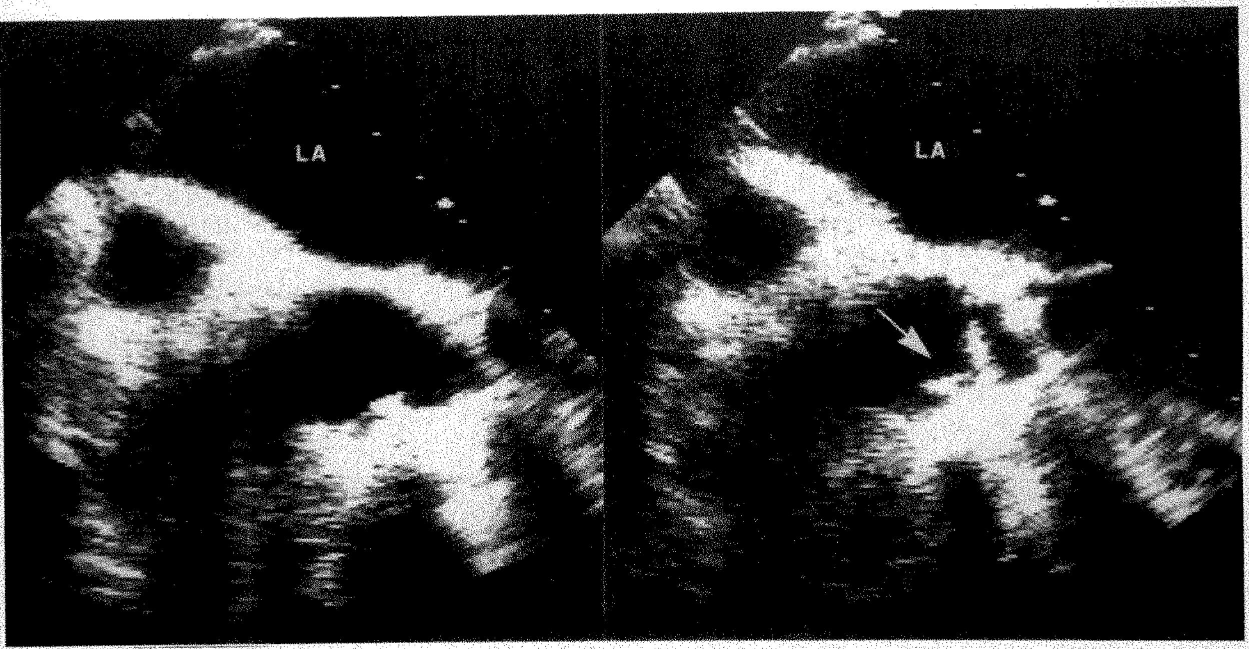

FIGURE 4. Diastolic (*left*) and systolic (*right*) views of a thrombosed, stenotic St. Jude aortic valve. Notice the nonparallel position of the semilunar discs (*arrow*) in midsystole due to thrombus that limited valve opening. LA = left atrium.

valvular pathology seen on TEE. Three of these patients were ≤35 years and thus did not undergo preoperative coronary angiography, thereby being spared a potentially hazardous procedure because of the bulky vegetations on the infected aortic valves. The improved resolution noted with TEE in describing and detecting anular and paravalvular lesions of the aortic valve is in keeping with case reports in which transesophageal echo detected sinus of Valsalva aneurysms associated with infected native and prosthetic aortic valves that were subsequently confirmed at surgery.[5,6] The ability of TEE to differentiate valvular from paravalvular aortic insufficiency in prosthetic valves is certainly an important advantage over surface echo where serious problems have been shown to exist, especially in the case of the Bjork-Shiley prosthesis.[10]

Visualization of the valve disc(s) in the case of Bjork-Shiley, Medtronic or St. Jude valves and valve leaflets in the case of tissue prostheses was accomplished in almost all cases, allowing discovery of a thrombus or vegetation in some and normal leaflet appearance in others. Other reports[2,7] have found that visualization of these structures from the transesophageal position is poor. The improved visualization in the cases presented here may have been due to unusual valve orientation or seating coupled with very heavy deposition of thrombotic or vegetative material. In 2 cases, it appeared that exaggerated motion of the vegetative material, seen from behind the prosthesis-induced attenuation into a clear imaging plane, allowed adequate visualization by TEE. Importantly, motion of both semilunar discs from a St. Jude prosthesis could be assessed, and diminished motion of both discs, as seen by TEE, was confirmed later by angiography and surgery.

The findings in this group of patients demonstrate the value of TEE in assessing prosthetic and native aortic valve disorders of various types and suggest that in some cases, evaluation by TEE is sufficient to allow surgical therapy without other invasive procedures.

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A Possible Mechanism for Neurologic Ischemic Events in Patients with Atrial Septal Aneurysm

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Atrial septal aneurysm (ASA) is a congenital malformation of the atrial septum that has been associated, among other conditions, with transient ischemic attacks and strokes.[1–5] The nature of this relation is unclear. Embolic events have been attributed to thrombus formation in or at the base of the aneurysmal sac.[5,6] However, the possibility of an associated functionally patent foramen ovale leading to a paradoxical embolus from a right-to-left shunting also has been suggested.[2–4] To help clarify this issue, we analyzed the morphologic and functional characteristics of the atrial septum in patients with ASA by the use of transesophageal contrast echocardiography.

From June 1989 to December 1989, 199 consecutive patients underwent clinically indicated transesophageal echocardiography at our medical center. Transesophageal echocardiography was indicated whenever the transthoracic study was nondiagnostic or inconsistent with the clinical status. The indications were to investigate intracardiac thrombus or masses in 105 patients (53%), prosthetic valves in 42 patients (21%), endocarditis in 32 patients (16%), mitral regurgitation in 15 patients (8%) and atrial septal abnormalities in 5 patients (3%). Twenty patients (10%) who had the echocardiographic criteria for ASA (see later) made up our study population. This group comprised 16 men and 4 women with a mean age of 59 ± 8 years. At the time of the study, 19 patients were in sinus rhythm and 1 was in atrial fibrillation. Clinical and laboratory data were obtained by personal interviews and a review of patients' charts.

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TABLE I Clinical and Echocardiographic Characteristics of Patients with Atrial Septal Aneurysm

Pt	Age (yrs) & Sex	TEE Indications	ASA Motion Without VM	ASA Motion With VM	Associated Conditions	Neurologic Events
1	79 M	TLS	Both atria	Left atrium	PFO	0
2	65 F	R/O atrial mass	Right atrium	Left atrium	PFO	0
3	63 M	SBE	Right atrium	Both atria	PFO	0
4	36 F	SOE	Both atria	Left atrium	PFO	+
5	60 M	R/O ASA	Both atria	Both atria	PFO/MVP	0
6	49 M	SOE	Both atria	Left atrium	PFO	+
7	61 M	TLS/SOE	Both atria	Left atrium	PFO	+
8	60 M	TLS	Both atria	Left atrium	PFO	0
9	80 M	R/O septal mass	Both atria	Left atrium	PFO	0
10	65 M	Assess MR	Both atria	Left atrium	PFO	0
11	30 M	AVR	Both atria	Left atrium	PFO	0
12	65 F	AVR	Both atria	Left atrium	PFO	0
13	66 M	R/O septal mass	Both atria	Left atrium	ASD	0
14	65 F	SOE	Right atrium	Left atrium	PFO	+
15	83 M	SBE	Both atria	Left atrium	PFO	0
16	62 M	SOE	Both atria	Left atrium	PFO/AF	+
17	48 M	SBE	Both atria	Left atrium	PFO/MVP	0
18	73 M	AVR	Both atria	Both atria	0	0
19	70 M	TLS/AVR	Left atrium	Left atrium	0	0
20	56 M	SOE/syncope	Both atria	Left atrium	PFO/RVE	+

AF = atrial fibrillation; ASA = atrial septal aneurysm; ASD = atrial septal defect; AVR = aortic valve replacement; MR = mitral regurgitation; MVP = mitral valve prolapse; PFO = patent foramen ovale; R/O = rule out; RVE = right ventricular enlargement; SBE = subacute bacterial endocarditis; SOE = source of emboli; TEE = transesophageal echocardiography; TIA = transient ischemic attack; TLS = technically limited transthoracic study; VM = Valsalva Maneuver.

During the same period, 2,059 echocardiographic studies were performed in the same medical center; this resulted in an overall prevalence of ASA of 1% in routine echocardiographic studies.

Esophageal examinations used 5.0 MHz phased-array transducers mounted on modified gastroscopes and interfaced to an RT 5000 (General Electric Medical System), or to an HP 77020 AC (Hewlett-Packard Ultrasound Systems). Patients fasted for a minimum of 6 hours. Glycopyrrolate 0.1 to 0.2 mg and midazolam hydrochloride 1.0 to 3.0 mg were given intravenously as premedication. Lidocaine in spray and viscous preparations was used to anesthetize the oropharyngeal area. With the patient lying in the left lateral decubitus position, the esophageal probe was introduced into the esophagus 30 to 35 cm distal to the patient's incisors. During satisfactory visualization of the interatrial septum, contrast study was achieved by injecting 10 cc of agitated 5% dextrose in water solution via an antecubital vein with and without Valsalva maneuver. All studies were reviewed by 2 independent observers unaware of the clinical data.

The presence of a patent foramen ovale was identified by the immediate appearance of microbubbles within the left atrium, after opacification of the right atrium by

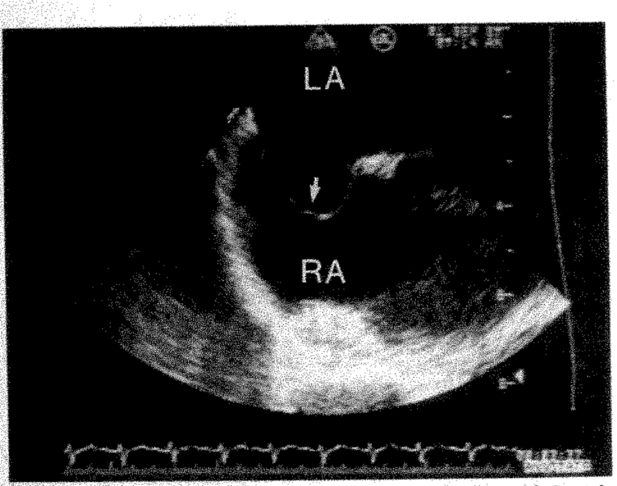

FIGURE 1. Transesophageal view of right atrium and left atrium. A typical case of atrial septal aneurysm is depicted. The redundant membrane of the septum primum *(arrow)* protrudes into right atrium in end-systole/early diastole. LA = left atrium; RA = right atrium.

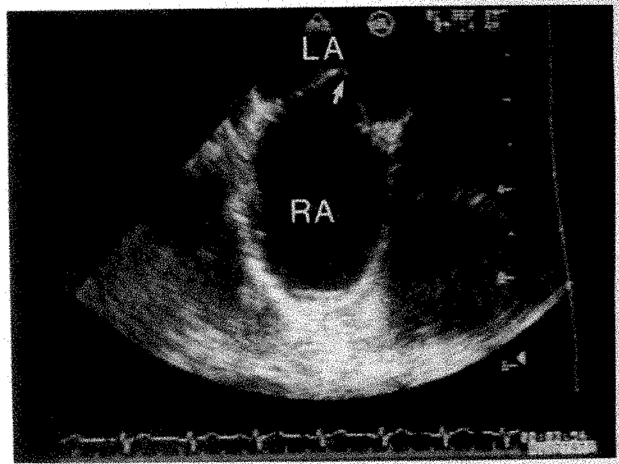

FIGURE 2. Transesophageal view of right atrium and left atrium. Same patient as in Figure 1. The redundant membrane of septum primum *(arrow)* now protrudes into left atrium in end-diastole/early systole. LA = left atrium; RA = right atrium.

means of contrast study. ASA was defined as a bulging of ≥1.5 cm of the atrial septum into the left, right or both atria (Figures 1 and 2) by means of transesophageal echocardiography.

Transesophageal echocardiography permitted high-resolution images in all 20 patients. In each patient, the fossa ovalis limbus formed by the septum secundum and the redundant membrane formed by the septum primum were clearly identified. All patients had an excellent opacification of the right atrium and right ventricle by means of contrast echocardiography. There were no discrepancies between the 2 observers regarding the presence of ASA and patent foramen ovale. Table I lists the clinical and echocardiographic features of the 20 patients with ASA. Two patients (10%) had ASA as an isolated finding; 1 patient (5%) had a small atrial septal defect that communicated into a large aneurysmal sac (Figure 3) and the remaining 17 patients (85%) had associated patent foramen ovale; 2 of these also had mitral valve prolapse and 1 had dilatation of the right-sided chambers.

In 1 patient (5%), the aneurysmal sac protruded only into the left atrium; in 3 patients (15%), it protruded only into the right atrium. However, in the remaining 16 patients (80%), its motion included both atria. In this latter group, a definitive motion pattern of the ASA was observed in relation to the cardiac cycle. In end-systole and early-diastole, the aneurysmal sac moved toward the right atrium and in end-diastole and early-systole, it moved toward the left atrium. However, this cyclic motion pattern was interrupted by the Valsalva maneuver. During the 10-second Valsalva strain, the aneurysmal sac persistently bowed toward the left atrium in 17 patients (85%) and toward both atria in the remaining 3 patients. In this series, no correlation was noted between the motion pattern of the ASA and the presence of neurologic events.

Five (25%) of the 20 patients had had documented ischemic brain events. In all these patients, an ASA was accompanied by interatrial right-to-left shunting. In 2 of these 5 patients (40%), additional underlying cardiac abnormalities were found (atrial fibrillation in 1, significant carotid artery disease in 1) that could account for the neurologic symptoms. In the other 3 patients (60%), an embolic origin was suggested on the basis of clinical presentation, computed tomography or arteriographic findings. One additional patient with patent foramen ovale and dilatation of the right atrium and right ventricle had a history of unexplained syncope. No patient had echocardiographic evidence of thrombus in any cardiac chamber, including the aneurysmal sac.

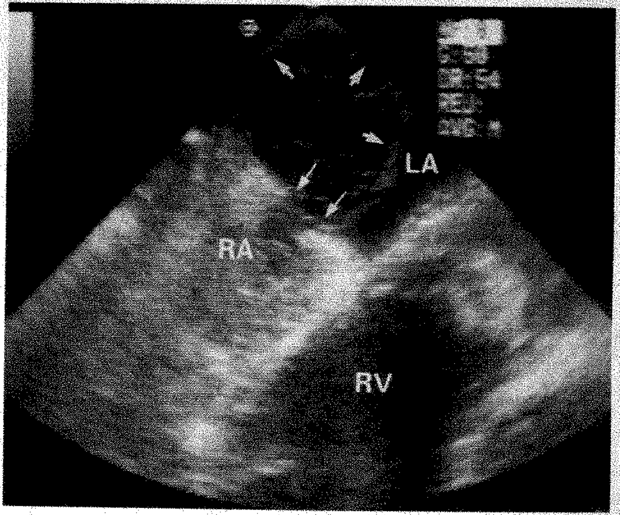

FIGURE 3. Transesophageal view of right atrium and left atrium. Right atrium is filled by microbubbles after contrast injection. A large atrial septal aneurysm within left atrium *(short arrows)* is being distended by microbubbles across an atrial septal defect *(long arrows)*. LA = left atrium; RA = right atrium; RV = right ventricle.

Our study presents the largest series of ASA assessed by transesophageal echocardiography. The observed prevalence of ASA in this series is similar to that reported by the largest autopsy series of ASA in adults,[6] that is, 1%. The reason for the higher prevalence in this study, compared to earlier studies[3,7] of ASA, may be improvement in ultrasound imaging, increased awareness of this abnormality and the recent availability of transesophageal echocardiography. The high incidence of patent foramen ovale associated with ASA in this series (85%) is in agreement with both pathologic[6,8] and echocardiographic[9] observations.

Our study confirms the previously suggested association between ASA and ischemic brain events. Although this study does not provide conclusive evidence of a causal relation between ASA and cerebrovascular emboli, the frequency of this association merits special consideration. We were unable to show thrombus in or around the aneurysmal septal sac as previously suggested in a necropsy series by Silver and Dorsey.[6] However, a high proportion of our patients had interatrial right-to-left shunting (85%). Certainly, paradoxic transseptal embolization of a venous-initiated thrombus is a possible explanation for the embolic association in this condition. A more difficult causal relation to prove between ASA and ischemic brain symptoms exists when the ASA is associated not only with interatrial shunting, but also with mitral valve prolapse, atrial fibrillation, mitral stenosis, valve prostheses or another independently recognized cause of systemic embolism.

Transesophageal contrast echocardiography strongly supports the premise that a paradoxical embolus is the most likely underlying mechanism to explain the relation between ASA and ischemic brain events. ASA should be considered in patients suspected of having an embolic arterial event without an obvious cardiac source. In these patients, contrast 2-dimensional echocardiography should be performed and evidence of ASA particularly sought.

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Effects of Left Ventricular Hypertrophy on the Signal-Averaged Electrocardiogram

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Signal-averaged electrocardiography (SAECG) has made possible the identification of late potentials in patients at risk of developing malignant ventricular arrhythmias.[1-9] Late potentials have been shown to predict sudden cardiac death,[3,4] clinical ventricular tachycardia,[1,3-6] and ventricular tachycardia that is inducible with programmed electrical stimulation.[8-10] Sudden cardiac death[11,12] and ventricular arrhythmias[13-19] are more prevalent in patients with echocardiographic left ventricular (LV) hypertrophy. Late potentials might be useful in identifying a subgroup of patients with LV hypertrophy who are at high risk to experience clinical ventricular tachycardia or sudden cardiac death. However, patients with LV hypertrophy may have intraventricular conduction disturbances and repolarization abnormalities that may interfere with the ability of SAECG to accurately detect late potentials. To evaluate the use of SAECG in patients with LV hypertrophy, we examined 58 patients with SAECG, echocardiography and programmed electrical stimulation. In this study, we compare the clinical characteristics, SAECG findings and electrophysiology results of a group of patients with echocardiographic LV hypertrophy to a group of patients without echocardiographic LV hypertrophy.

The records of approximately 1,000 patients who underwent SAECG were reviewed and patients who had undergone echocardiography and programmed electrical stimulation were selected. Patients were excluded if they had Wolff-Parkinson-White syndrome, bundle branch block or a pacemaker. Patients were also excluded if the M-mode echocardiogram was technically inadequate or if they were on antiarrhythmic therapy.

SAECGs were recorded after careful skin preparation and the application of silver-silver chloride electrodes. The Arrhythmia Research Technology model 101 or model 1200 EPX machines were used to record orthogonal X, Y and Z leads. The signal from each lead was amplified 1,000 times and converted from analog to digital form at 16-bit accuracy with a sampling rate of 1,000 Hz. Ectopic or noisy beats were rejected by a recognition template generated from the first 8 beats. At least 150 beats were averaged in each recording with a noise level <1.0 mV.

After signal-averaging, the data was filtered using a bidirectional digital filter with a bandpass of 40 to 250 Hz. The 3 leads were combined in a root-mean-square vector ($V = (x^2 + y^2 + z^2)^{0.5}$*), which was termed the filtered QRS (Figure 1). The beginning and end of the filtered QRS were determined by computer algorithm to eliminate operator bias. Four SAECG parameters were examined and compared between patient groups. These parameters included the filtered QRS duration, the duration of the terminal QRS or low amplitude signal <40 mV (LAS duration), the root-mean-square of the terminal 40 ms (RMS LAS), and the root-mean-square amplitude of the filtered QRS (RMS QRS). Normal values for these parameters are listed in Table I. Late potentials were considered present if 2 of the first 3 parameters (QRS duration, LAS duration and RMS LAS) were abnormal.*

M-mode echocardiographic measurements of the ventricular septum, posterior wall and LV end-diastolic dimension were made according to recommendations of the American Society of Echocardiography.[20] The LV mass was calculated using an anatomically validated modification of the Penn Convention and indexed to body surface area.[21,22] LV hypertrophy was considered

TABLE I Comparison of Signal-Averaged Electrocardiogram Parameters in Patients With and Without LVH

	Normal Value	With LVH	Without LVH	p Value
QRS duration (ms)	<120	122 ± 22 (88 to 180)	103 ± 16 (70 to 134)	NS*
LAS duration (ms)	<40	35 ± 19 (3 to 88)	30 ± 12 (8 to 53)	NS
RMS LAS (uV)	>25	31 ± 21 (8 to 98)	37 ± 27 (7 to 103)	NS
RMS QRS (uV)		60 ± 29 (25 to 137)	63 ± 24 (21 to 140)	NS

* p = 0.09.
LAS duration = duration of low amplitude signal (<40 mV) in terminal QRS; LVH = left ventricular hypertrophy; NS = not significant; QRS duration = duration of filtered QRS; RMS LAS = root-mean-square amplitude of last 40 ms of QRS; RMS QRS = root-mean-square amplitude of filtered QRS.

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TABLE II Baseline Clinical Characteristics and Echocardiographic Left Ventricular Mass

	With LVH (%)	Without LVH (%)	p Value
Number	21	37	
Age (yrs)	61 ± 15	58 ± 15	NS
Men	16 (76)	29 (78)	NS
Women	5 (24)	5 (22)	NS
Myocardial infarction by history	15 (71)	19 (51)	NS
Anterior myocardial infarction	8 (38)	9 (24)	NS
Inferior myocardial infarction	7 (33)	9 (24)	NS
Both	0	1 (3)	NS
LV mass (g)	176 ± 68	91 ± 22	0.00001
Sudden cardiac death	6 (29)	7 (19)	NS
Clinical ventricular tachycardia	8/19 (42)	16/35 (46)	NS
Inducibility	14 (66)	20 (54)	NS

* Data unavailable for 2 patients in each group.

TABLE III Statistical Association Between Individual and Combined Signal-Averaged Parameters with Clinical Events in Patients With and Without Left Ventricular Hypertrophy

	With LV Hypertrophy			Without LV Hypertrophy		
	IND	CVT	SCD	IND	CVT	SCD
QRS Duration*	NS	NS	NS	0.062	NS	NS
LAS Duration*	NS	NS	NS	0.000	0.111	NS
RMS 40 (ms)*	NS	NS	NS	0.000	0.016	NS
RMS QRS*	NS	NS	NS	0.002	0.016	NS
Combined late potentials†	NS	NS	0.04	0.001	0.025	NS

* Compared to clinical events using analysis of variance; † compared to clinical events using chi-square test.
CVT = clinical ventricular tachycardia; IND = inducible ventricular tachycardia; NS = not significant; SCD = sudden cardiac death. Other abbreviations as in Table II.

present if LV mass was >134 g/m^2 for men or >110 g/m^2 for women.

Electrophysiologic testing was performed in using a previously described protocol.[8] The endpoint of the stimulation protocol was the reproducible induction of a sustained monomorphic ventricular tachycardia. In patients with polymorphic ventricular tachycardia or ventricular fibrillation, stimulation was stopped if countershock was required.

Continuous data is expressed as the mean ± standard deviation and compared with one-way analysis of variance. Proportions were compared with the chi-square statistic. A p value ≤0.05 was considered statistically significant.

Fifty-eight patients had SAECG, M-mode echocardiography and programmed electrical stimulation. Twenty-one patients had echocardiographic LV hypertrophy; 37 patients did not (Table II). The 2 patient groups were similar in age, sex, incidence of myocardial infarction, inducible ventricular tachycardia, clinical ventricular tachycardia, and sudden cardiac death.

When comparing patients with LV hypertrophy to patients without LV hypertrophy there were no statistically significant differences in the QRS duration, LAS duration, RMS LAS or the RMS QRS (Table I). However, the QRS duration was slightly longer in patients with LVH (122 ± 22 ms vs 103 ± 16 ms, $p = 0.09$).

No individual SAECG parameter was significantly associated with inducible ventricular tachycardia in patients with LV hypertrophy (Table III). However, 3 of the 4 individual SAECG parameters (LAS duration, RMS LAS and RMS QRS) were significantly associated with inducible ventricular tachycardia in patients with no LV hypertrophy, and the association of QRS duration to inducible ventricular tachycardia was close to statistical significance ($p = 0.06$). Late potentials were not associated with inducible ventricular tachycardia ($p = 0.2$) in patients with LV hypertrophy, but in patients without LV hypertrophy, late potentials were significantly associated with inducibility ($p = 0.001$).

Similarly, no individual SAECG parameter was significantly associated with clinical ventricular tachycardia in patients with LV hypertrophy (Table III). However, in patients with no LV hypertrophy, the RMS LAS and RMS QRS were significantly associated with clinical ventricular tachycardia ($p < 0.02$). QRS duration and LAS duration also tended to correlate with clinical ventricular tachycardia ($p = 0.19$, $p = 0.11$, respectively). Late potentials showed no association with clinical ventricular tachycardia in patients with LV hypertrophy, but they were significantly associated with clinical ven-

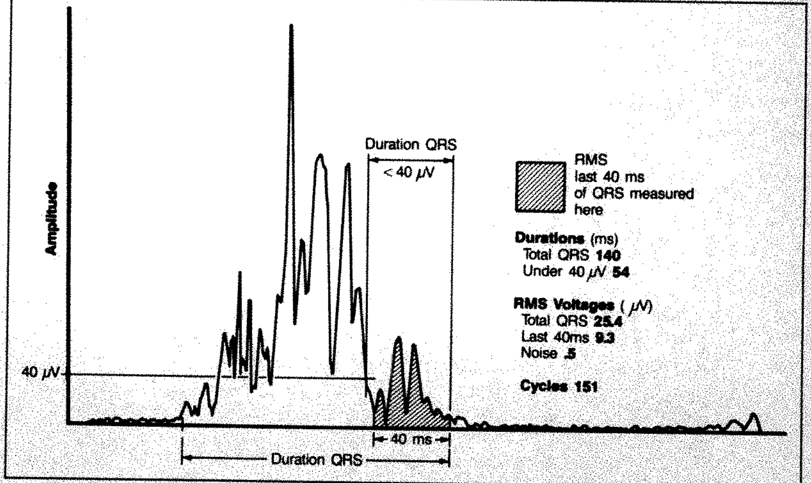

FIGURE 1. An example of a recording with a late potential. The measurements used in this analysis are shown. The RMS QRS is the area *(unshaded and shaded)* under the QRS curve. (Reproduced with permission from *Am J Cardiol.*[23])

tricular tachycardia in patients with no LV hypertrophy ($p = 0.025$).

No individual SAECG parameter had a statistically significant association with sudden cardiac death in either group (Table III). Late potentials were associated with sudden cardiac death in patients with LV hypertrophy ($p = 0.04$) but not in patients without LV hypertrophy (difference not significant).

SAECG has made possible the identification of patients at high risk of developing ventricular arrhythmia; however, clinical use of SAECG has been limited by borderline sensitivity, specificity and predictive value of this test as a predictor of serious clinical events.[3] The clinical use of SAECG testing might be improved if high-risk populations are tested. Patients with LV hypertrophy represent such a high-risk population[11-19]; however, our results show that LV hypertrophy may interfere with and subtract from the association between SAECG parameters and ventricular arrhythmias.

Previous studies have shown the ability of SAECG to predict clinical ventricular tachycardia,[3-6] inducible ventricular tachycardia[8-10] and sudden cardiac death.[3] However, no previous studies have separately analyzed patients with LV hypertrophy. Based on our findings, the exclusion of patients with LV hypertrophy may improve the ability of SAECG to predict inducible ventricular tachycardia and clinical ventricular tachycardia, but not sudden cardiac death.

The fact that combined abnormal SAECG parameters (late potentials) were associated with sudden cardiac death only in patients with LV hypertrophy and not in patients without LV hypertrophy may reflect the higher incidence of sudden cardiac death in patients with echocardiographic[11,19] and electrocardiographic[12] LV hypertrophy. Positive late potentials in patients with LV hypertrophy may identify a subgroup of these patients at higher risk for sudden cardiac death. Prospective studies will be needed to confirm this.

The inducibility of sustained monomorphic ventricular tachycardia by programmed electrical stimulation is a reliable clinical endpoint for guiding antiarrhythmic therapy. Moreover, we feel that the high degree of association between individual and combined SAECG parameters and inducible ventricular tachycardia in patients without LV hypertrophy and the absence of such an association in patients with LV hypertrophy is the most significant finding in this study.

The most important limitations of our study relate to the small size and highly selected nature of the study population. Data derived from a small population of patients who have undergone programmed electrical stimulation cannot be extrapolated to the population at large. Our findings may be most useful in the interpretation of SAECGs on patients being considered for programmed electrical stimulation.

Thus, individual and combined SAECG parameters are significantly associated with inducible ventricular tachycardia and clinical ventricular tachycardia in patients without echocardiographic LV hypertrophy but not in patients with echocardiographic LV hypertrophy. These data suggest that LV hypertrophy interferes with the usefulness of this test for identifying patients at risk for ventricular arrhythmia. Further work will be required to determine the mechanism for this interference and to see if the findings are consistent in more general patient populations.

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Argon Laser Ablation or Modification of the Atrioventricular Conduction System in Refractory Supraventricular Tachycardia

Sanjeev Saksena, MD, and Isaac Gielchinsky, MD

Management of drug-refractory supraventricular tachycardia has been greatly facilitated by several nonpharmacologic therapeutic options. These options include catheter or surgical ablation of the arrhythmogenic substrate or the use of antitachycardia pacemakers. Catheter ablation is performed for interruption or modification of normal or abnormal atrioventricular (AV) conduction using direct current shocks or radiofrequency energy.[1] Intraoperative ablation of these conduction pathways is now only performed in the following cases: in symptomatic patients who have either failed catheter ablation; concomitantly with cardiac surgery for another indication; or in place of catheter ablation in specific conditions, for example, preexcitation syndromes. Implantation of antitachycardia devices is usually restricted to a few highly selected patients. Experimental studies have suggested that argon laser ablation of the specialized AV conduction system or accessory pathways is feasible.[2,3] Since 1986, we have used catheter delivery of argon laser energy for intraoperative ablation of malignant supraventricular and ventricular tachycardia.[4-6] We have previously reported its use in supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome.[5,7] In this study, we report our initial clinical experience with normothermic argon laser catheter ablation of the specialized AV conduction system and examine its clinical electrophysiologic effects.

Patient 1, a 68-year old woman with chronic recurrent supraventricular tachycardia, coronary artery disease and old anterior myocardial infarction was admitted with a new regular wide QRS complex tachycardia. Electrophysiologic study showed dual antegrade AV nodal conduction pathways. Single atrial extrastimuli induced sustained AV nodal reentrant tachycardia at a cycle length of 370 to 400 ms with intermittent right bundle branch block and sustained sinus node reentrant tachycardia with a cycle length of 540 ms with 1:1 AV conduction. Single and double ventricular extrastimuli also induced both supraventricular tachyarrhythmias. The antegrade effective refractory period of the AV node was 320 ms. Rapid ventricular pacing also induced sustained ventricular tachycardia with a cycle length of 260 ms with AV dissociation. Serial drug testing was undertaken. Supraventricular and ventricular tachycardia remained inducible or incessantly recurred on oral digoxin, nadolol, quinidine, recainam, propafenone, verapamil and mexiletine; the patient was intolerant of procainamide and quinidine. Cardiac catheterization revealed total occlusion of the left anterior descending artery with dyskinesia of the anterolateral and apical left ventricle. Preoperative left ventricular ejection fraction was 37%. Catheter endocardial mapping of 2 ventricular tachycardia morphologies was performed. Intraoperative mapping-guided laser ablation was recommended for both tachycardias. Written informed consent was obtained. After cannulation for cardiopulmonary bypass, a right atriotomy was performed using pulsed laser energy and endocardial mapping of the low right atrium was performed to define the Bundle of His. Mapping was continued superiorly to define the upper limit of the His bundle and the adjoining AV nodal region. Pulsed argon laser ablation of the AV nodal region was performed in a normothermic state. Pulse duration was 0.5 second with interpulse intervals of 0.3 second. Total delivered energy was 381 J and area of ablated region was 1.1 cm^2 with an energy density of 346 J/cm^2. During and after laser irradiation, the patient developed complete AV block with an accelerated junctional rhythm with a cycle length of 750 ms (Figure 1A). The right atriotomy was sutured and ventricular tachycardia mapping and laser endocardial ablation was undertaken.[6] Postoperatively, the patient recovered 1:1 AV conduction within 24 hours. First degree AV block was noted during sinus rhythm and atrial pacing QRS morphology was unchanged from preoperative recordings. Antegrade AV nodal effective refractory period and Wenckebach point prolonged to 380 ms at postoperative electrophysiologic study. Atrial and ventricular stimulation failed to initiate AV nodal reentrant tachycardia or ventricular tachycardia. Six sinus node reentrant echo beats were initiated with ventricular extrastimulation. Postoperatively, spontaneous atrial flutter occurred with 2:1 AV block and a ventricular cycle length of 470 ms in the absence of antiarrhythmic drugs. It was electrically cardioverted and the patient was placed on digoxin. Holter monitoring revealed sinus rhythm with stable first degree AV block (Figure 1B). Exercise testing revealed no inducible supraventricular or ventricular tachycardia with 1:1 AV conduction up to 130 beats/min. After exercise, she had nonsustained atrial flutter/fibrillation. Permanent pacing was not recommended. After discharge, she was withdrawn from digoxin. Subsequent Holter monitoring revealed nonsustained episodes of a regularly irregular atrial tachycardia and 1 episode of sustained tachycardia lasting 1 minute with an average rate of 130 beats/min consistent with atrial flutter with variable block. Verapamil therapy suppressed this arrhythmia. Clinical follow-up of 33 months shows continued suppression

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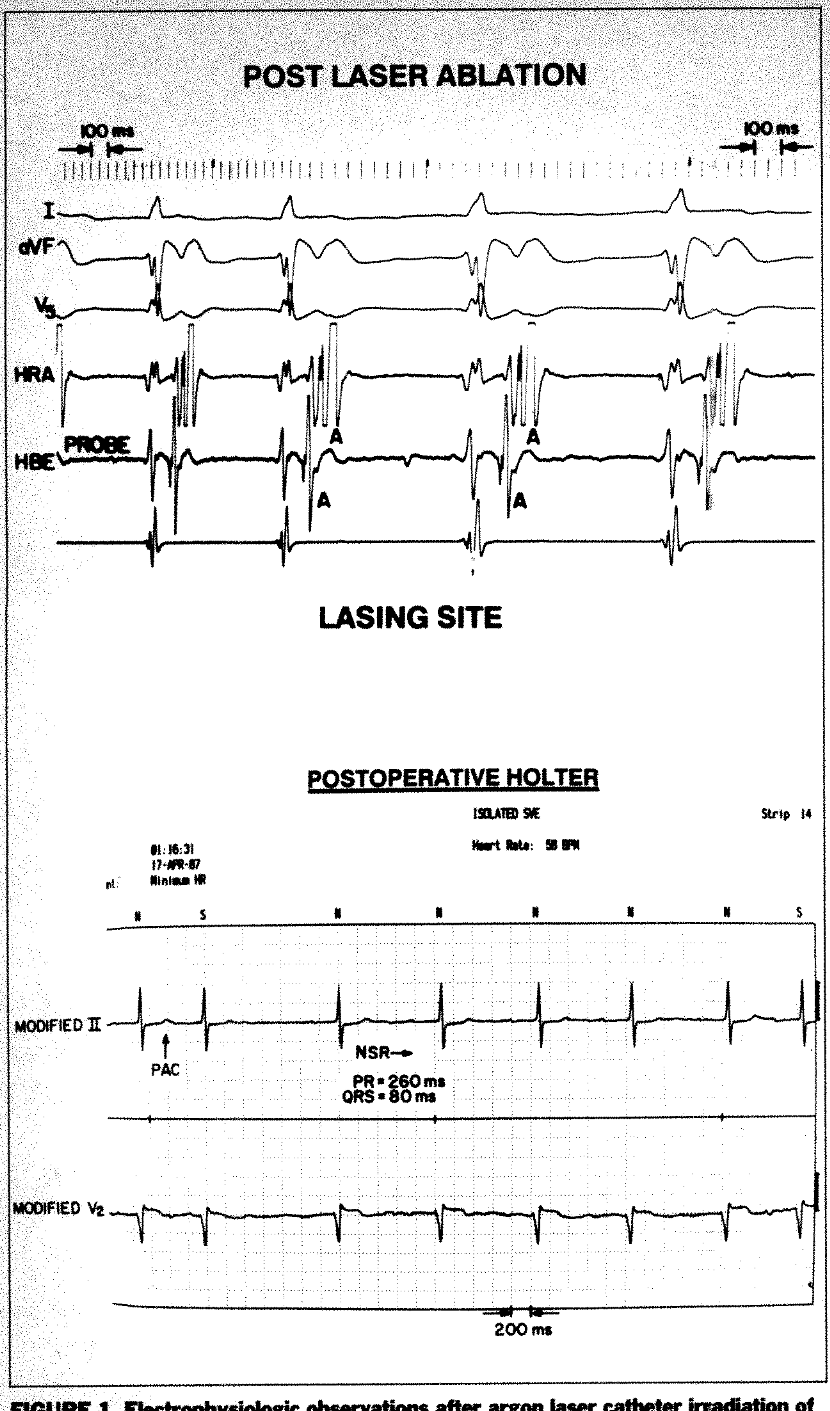

FIGURE 1. Electrophysiologic observations after argon laser catheter irradiation of the atrioventricular node in a patient with atrioventricular nodal reentrant tachycardia. *Top*, intraoperative recordings of surface electrocardiogram and intracardiac electrograms immediately after pulsed argon irradiation. Surface electrocardiogram leads I, aVF and V_5 are shown along with high right atrial electrogram and recordings from a bipolar probe in the His bundle region. Immediately after laser irradiation, the patient developed the accelerated junctional rhythm shown in the tracings at a cycle length of 750 ms with retrograde atrial activation being readily apparent. The surface QRS morphology is unchanged from preablation appearance. Postoperatively, the patient remained in junctional rhythm with a narrow QRS complex for a few hours before reverting to sinus rhythm with first-degree atrioventricular nodal block. *Bottom*, postoperative Holter monitor obtained after argon laser catheter modification of atrioventricular nodal conduction in a patient with atrioventricular reentrant tachycardia. Note that sinus rhythm with first degree atrioventricular block with a narrow QRS complex is present. A premature atrial contraction fails to initiate supraventricular tachycardia that was incessantly induced by atrial premature beats preoperatively. A = atrial electrogram; HBE = His bundle electrogram; HRA = high right atrium; NSR = normal sinus rhythm; PAC = premature atrial contraction; SVE = supraventricular ectopic.

of all supraventricular tachycardias and ventricular tachycardia.

Patient 2, a 60-year-old woman, was admitted for palpitations and presyncope. Atrial tachyarrhythmias with ventricular rates ranging from 200 to 250 beats/min were documented. Electrophysiologic studies documented inducible intraatrial reentrant tachycardia and atrial flutter with 1:1 AV nodal conduction up to cycle lengths of 250 ms and left bundle branch block. No ventriculoatrial conduction was present. Atrial fibrillation was also induced with the shortest RR interval being 200 ms. Digoxin, metaprolol, disopyramide and nadolol alone and in combination were unable to control the tachycardia. Two catheter ablation procedures using direct current shocks were unsuccessful. The preoperative PR interval was 150 ms. Using similar mapping techniques as in Patient 1, the Bundle of His was identified. Pulsed argon laser ablation was performed using both a sapphire lens-tipped probe and a polished 300-micron quartz optical fiber superior to this location, above the medial leaflet of the tricuspid valve. This produced PR prolongation up to 280 ms but atrial pacing-induced Wenckebach still occurred at cycle length of 360 ms. Laser irradiation was then performed more inferiorly just below the tricuspid annulus and resulted in immediate complete AV block with a junctional escape rhythm at 55 beats/min. Total delivered energy was 1462 J and the area of ablation was 1.3 cm^2 with an energy density of 1124 J/cm^2. The patient remained in this rhythm postoperatively. Electrophysiologic studies performed after 10 days revealed persistent complete AV nodal block not reversed by atropine (Figure 2). A rate-responsive demand ventricular pacemaker was implanted. There has been no recurrent supraventricular tachycardia and complete AV block persists on Holter monitoring during a 32-month followup. Postoperative left ventricular ejection fraction was 72%.

Patient 3, a 62-year-old obese diabetic woman, was admitted for unstable angina, recurrent refractory supraventricular tachycardia and congestive heart failure. Cardiac *catheterization revealed severe 3-vessel coronary artery disease, posterobasal left ventricular akinesis and a cardiac index of 2.1 liters/min/m^2. Coronary artery bypass surgery was recommended. Preoperative electrophysiologic evaluation revealed automatic atrial tachycardia with rate-related left bundle branch block. The antegrade AV nodal effective refractory period was ≤240 ms. The atrial tachycardia remained uncontrolled despite digoxin, propranolol, quinidine and verapamil therapy alone or in combination. Intraoperative laser ablation of the AV conduction system was recommended at the time of coronary bypass surgery. His bundle mapping and laser ablation was performed as described above in the normothermic heart. Laser irradiation resulted in persistent complete AV block with an escape idioventricular rhythm with a cycle length of 1,130 ms. Total delivered energy was 588 J over an ablation area of 1.5 cm^2 for an energy density of 392 J/cm^2. Coronary artery bypass surgery was completed. Postoperative AV sequential pacing was instituted. Atrial tachycardia recurred and 3:1 or 4:1 AV conduction patterns were observed. Electrophysiologic study performed after 7 days revealed sinus rhythm with first-degree AV nodal block. The AH interval was 175 ms and the HV interval 50 ms. The Wenckebach point was 380 ms. Atrial flutter was associated with 4:1 or 3:1 AV conduction and after conversion, third-degree AV nodal block was observed (Figure 3). Postoperatively, she developed pedal edema and bilateral deep vein thrombophlebitis. She was started on digoxin, furosemide and intravenous heparin but developed episodic recurrent precordial pain. Atrial flutter/fibrillation recurred with an average ventricular rate of 130 beats/min and was now controlled on verapamil. On the nineteenth postoperative day, she developed sudden dyspnea and chest pain without supraventricular arrhythmia. She died in acute respiratory distress. Acute or recurrent pulmonary embolism was suspected but an autopsy was declined.*

Control of supraventricular tachycardia by surgical interruption of the specialized AV conduction system was reported over 2 decades ago.[8,9] Surgical intervention is highly effective and has a low risk.[10] Catheter ablation with direct current shocks is also clinically effective.[11] Accessory pathway ablation remains possible in selected locations only due to concern regarding safety.[12] Safer and more precise alternative energy sources are in development. Radiofrequency current and laser energy have been suggested for this purpose.[13,14] Acute and chronic electrophysiologic effects of argon laser irradiation of the AV node can be evaluated from our data. Pulsed laser irradiation in the normothermic heart produces precise interruption of the AV nodal conduction once the beam is correctly guided by endocardial mapping. Enhanced junctional automaticity was observed in 1 patient while a junctional or idioventricular escape rhythm was also noted in the other patients. Partial recovery of AV nodal conduction with modification occurred in 2 patients who received energy densities of 346 J/cm^2 and 392 J/cm^2. Complete AV nodal block persisted in patient 2 who received high laser energy density; this was not reverted by atropine or exercise. Postoperative atrial arrhythmias, often observed in cardiac surgical patients, were controlled with preoperatively ineffective drug therapy in both patients with modified AV nodal conduction. Thus, analysis of our electrophysiologic findings suggests that long-term in-

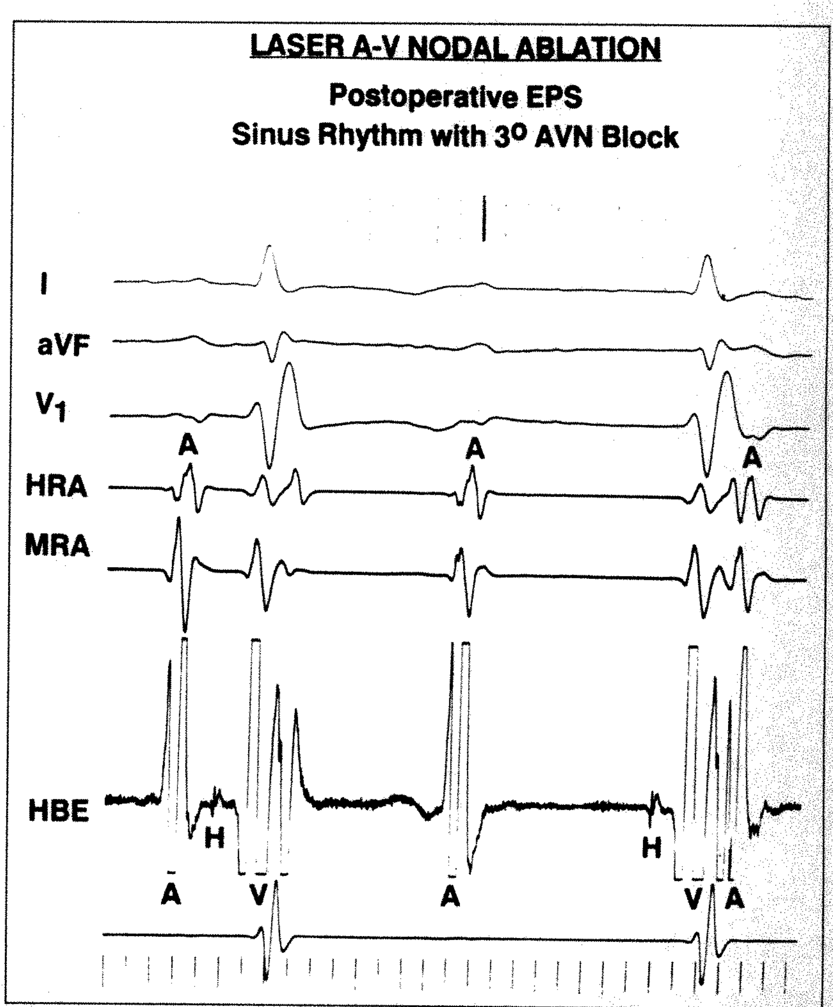

FIGURE 2. Postoperative electrophysiologic study in a patient with refractory atrial tachycardia with rapid atrioventricular nodal conduction. Preoperative direct current shock ablation was unsuccessful and had resulted in a right bundle branch block QRS pattern. After laser catheter ablation, third-degree atrioventricular nodal block appeared. Postoperative recordings show sinus rhythm with complete atrioventricular nodal block. A = atrial electrogram; AVN = atrioventricular node; EPS = electrophysiologic study; H = His bundle electrogram; HBE = His bundle electrogram; HRA = high right atrium; MRA = midright atrium; V = ventricular electrogram.

terruption or modification of AV nodal conduction is feasible with argon laser energy. We have previously showed similar conduction block in accessory pathways and ventricular tachycardia substrates.[6,7] There were no deleterious hemodynamic or mechanical adverse events during or immediately after laser irradiation. The role of laser ablation in the genesis of possible pulmonary embolism on patient 3 needs comment. The postoperative clinical course was complicated by lower extremity deep-vein thrombophlebitis after saphenous vein harvesting. Paroxysmal atrial arrhythmias, even with a controlled ventricular rate, may also initiate thrombogenesis. While these 2 conditions are the most common etiologies for postoperative embolic phenomena, the possibility of thrombogenesis at the lasing site cannot be eliminated. Postoperative echocardiograms performed in over 40 patients with ventricular tachycardia and supraventricular tachycardia with Wolff-Parkinson-White syndrome have, however, in our experience failed to show evidence of any endocardial thrombus at the lasing site.[6] Argon laser-induced myocardial perforation was not observed. Our experience suggests that pulsed laser irradiation may provide a precise and effective energy source for percutaneous catheter ablation of the AV conduction system. It has no barotraumatic effect and protection of the quartz optical fiber tip from thermal damage is possible.[15] We used a sapphire lens-tipped quartz optical fiber for this purpose in patient 2. Transmission through a blood-filled medium could also dissipate beam effects and effective energy delivery. Experimental studies have, however, suggested that the thermal effects of laser energy can be enhanced in a blood medium.[16] Laser energy, unlike radiofrequency current, can be effectively applied without direct tissue contact in a normothermic beating heart. Sequential lesions can produce a lesion of defined size and effect. Furthermore, electrophysiologic effects can be simultaneously monitored. Effective ablation of normal and diseased myocardium has been feasible.[17] Radiofrequency current has been less effective in diseased human tissues.[18] While our studies suggest that laser energy may be a suitable clinical ablation energy source, specialized catheter delivery systems for mapping the arrhythmogenic substrate and accurate delivery of the ablation energy remain to be developed for percutaneous use.

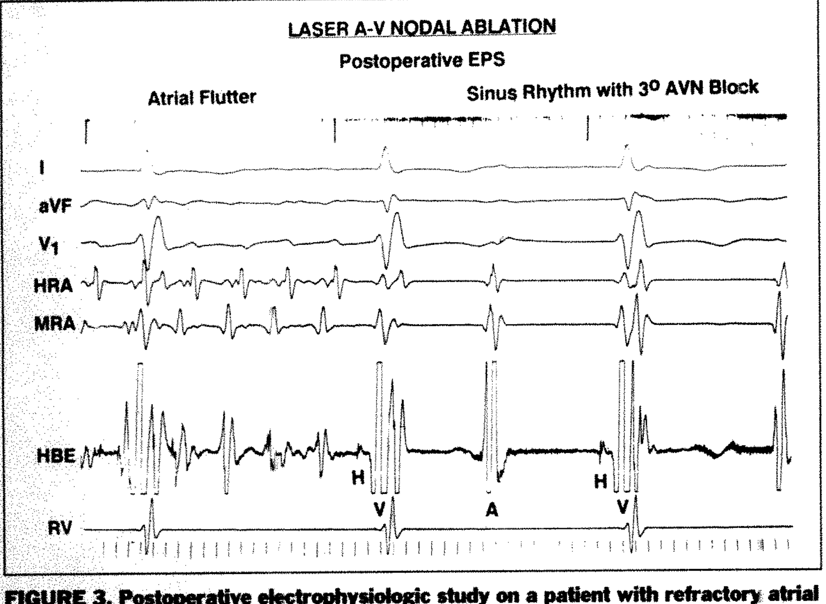

FIGURE 3. Postoperative electrophysiologic study on a patient with refractory atrial tachycardia after laser catheter modification of the atrioventricular node. After coronary bypass surgery, which included an atriotomy, the patient developed recurrent atrial flutter as well as atrial tachycardia. Postoperative recordings show atrial flutter with a high degree atrioventricular nodal block and a controlled ventricular rate. Upon spontaneous termination of atrial flutter, sinus rhythm with high-degree atrioventricular nodal block is observed. Resting electrocardiograms show sinus rhythm with first-degree atrioventricular nodal block. RV = right ventricular electrogram; other abbreviations as in Figure 2.

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READERS' COMMENTS

Misleading Subgroup Analyses in GISSI

The GISSI study[1] of streptokinase in acute myocardial infarction is one of the most important randomized trials ever conducted and when it was published it provided the best evidence then available that thrombolytic therapy reduced mortality. But the ability of the GISSI report to save lives could be substantially compromised by misinterpretation by clinicians of some of the data-dependent subset analyses that it contained. The problem of inappropriate interpretation of analyses of subsets of the GISSI data may, moreover, be aggravated by a recent publication[2] of some GISSI data that makes the statistically unjustified claim that "there could be a threshold phenomenon of 4-lead involvement for beneficial effects" of streptokinase. The only evidence presented to "support" this claim was that if a standard 12-lead electrocardiogram was used to subdivide patients into 4 infarct-extent categories (<4, 4 to 5, 6 to 7, >7 affected electrocardiogram leads), the streptokinase-associated reductions in the odds of death ± 1 standard deviation were 12% ± 13, 35% ± 12, 31% ± 12 and 24% ± 12, respectively.

The authors, however, argue that because the first of these reductions, considered in isolation, is not conventionally significant, they may have discovered a threshold of electrocardiogram involvement below which streptokinase does not save lives. Quite apart from the biological implausibility of such a threshold, there is not even statistically reliable evidence of *any* real trend between these 4 percentages (test for trend = 0.6 standard deviations, $p > 0.5$). Thus, GISSI provides no good evidence of even a "quantitative" difference between the sizes of these percentages, let alone any good evidence of a "qualitative" difference (whereby the effect is zero in one category but not in the others).

The unreliability of data-dependent subset analyses of clinical trials was discussed in the report of the ISIS-2 trial of streptokinase plus aspirin,[3] where it was noted that such analyses are likely to generate numerous false negative results. One example considered there was the question of whether streptokinase could reduce mortality not only in patients with a first infarct but also in patients with a history of previous infarction. Subgroup analyses of one trial[1] said it did not, subgroup analyses of another trial[3] said its absolute benefits among such patients were particularly large, while subgroup analyses of the combined data from both studies indicated significant benefit in both subcategories (as, perhaps more importantly, did qualitative extrapolations from the overall results of both studies to the subcategories with and without prior myocardial infarction). Another example was astrology: subgroup analyses[3] suggested treatment to be ineffective in patients born under Libra or Gemini, but highly effective in other patients! It is to be hoped that few doctors will let this astrological "finding" directly influence who they treat, but if it helps discredit data-dependent subgroup analyses then it may indirectly influence the treatment of many patients, saving some lives.

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More generally, since thrombolytic treatments do on balance save lives, it is a serious business to claim that a group has been identified who should be denied such therapy, and such claims should therefore be made only if there is statistically serious evidence supporting them (i.e., supporting a *qualitative* interaction). In this context, a trend that is 0.6 standard deviations away from zero should certainly not qualify as serious evidence. Subgroup analyses are fine, as long as appropriate statistical considerations[4-6] are used to interpret them. At present, however, there is a danger that the subgroup analyses of the GISSI investigators will somewhat undermine the remarkable achievement that the overall results of GISSI originally represented.

Richard Peto, FRS
Oxford, England
19 September 1989

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REPLY: The human and economic resources involved in carrying out a large-scale trial such as GISSI[1] allow us to obtain a lot of information, which all good clinicians should use to better understand biological and clinical phenomena and to prepare future research hypotheses. It would be too limiting to reduce the results of such a large-scale trial to a simple comparison of the differences in mortality rates between two groups (control vs treated patients), particularly as these results are so clear that they do not require any further comment. It was for these reasons that we evaluated the GISSI electrocardiograms and presented the results in *The American Journal of Cardiology*.[2]

The criticisms contained in Dr. Peto's letter seem to have been prompted by a too clear-cut definition of some of the results of our statistical analyses, the main conclusions of which can be summarized as follows: (1) Standard electrocardiography, a simple and widely used method, may provide a good prognostic index in cases of acute myocardial infarction (AMI). (2) The extent of AMI revealed by the 12-lead electrocardiogram has a greater prognostic power than the site of infarct, regardless of the therapy used. (3) The reduction in mortality in the streptokinase group is statistically significant in patients with 4 to 5, 6 to 7 and 8 to 9 leads involvement while, in those with small infarcts, there was a positive trend (6.1 streptokinase patients vs 6.8 control subjects) although it did not reach statistical significance, "*at least in terms of mortality*." Mortality rate is too gross an index to reveal smaller benefits and might generate a "threshold effect" which, we agree, is hardly plausible. In small infarcts, there could be a significant improvement in terms of the preservation of ventricular function but any evaluation of this would require the use of more sophisticated methods, such as 2-D echocardiography or nuclear angiography. In any case, we would like to emphasize that we never suggested that our data might lead to the identification of "a group who should be denied thrombolytic therapy," as Dr. Peto says. We agree that it is necessary to avoid misleading interpretation of an exploratory subgroup analysis planned a posteriori, which might be understood as implying clinical behaviors contradicting the main results of the study, *but this is not the case here.* Furthermore, since we consider clinical trials to be useful tools in understanding biological phenomena, the question of an electrocardiogram-based prognostic classification of patients undergoing thrombolysis was prospectively included among the objectives of the GISSI-2 study.[3]

Francesco Mauri, MD
Maurizio Gasparini, MD
Lorella Barbonaglia, MD
Eugenio Santoro, MD
MariaGrazia Franzosi, MD
Gianni Tognoni, MD
Fausto Rovelli, MD
Milan, Italy
20 November 1989

1. Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet 1986;1:397-401.*

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ed by streptokinase (the GISSI trial). *Am J Cardiol 1989;63:1291–1295.*
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More Questions on Kussmaul's Sign

The study by Meyer et al[1] on the mechanism of Kussmaul's sign sheds light in a confusing realm. Questions in 2 areas occur.

First, is the increased abdominal pressure the prime mover in Kussmaul's sign? If so, would every patient with hepatojugular reflux exhibit a Kussmaul's sign if sufficiently deep and slow breaths were taken? Have there been studies to determine the frequency of either sign without the other, or the relative sensitivity and specificity of each? Further comments on the interrelation of hepatojugular reflux and Kussmaul's sign might clarify what physiology they share and how they differ.

Second, is it known why Kussmaul's sign is *not* characteristic of pericardial tamponade? It seems that the 2 factors that Meyer et al identify as contributing to the sign in its diverse settings—inelasticity of the heart or pericardium and a distended venous system—exist in tamponade as well: the fluid stretches the serous membrane such that it no longer moves with the cardiac cycle. Shouldn't Kussmaul's sign appear in tamponade as well? Does its failure to do so provide any further pathophysiologic insight?

Henry Schneiderman, MD
Farmington, Connecticut
1 December 1989

1. Meyer TE, Sareli P, Marcus RH, Pocock W, Berk MR, McGregor M. Mechanism underlying Kussmaul's sign in chronic constrictive pericarditis. *Am J Cardiol 1989;64:1069–1072.*

REPLY: The comments and questions raised by Schneiderman underscore the confusion that exists about the pathophysiology of Kussmaul's sign and its association with various disease states. This sign, as we understand it, describes 2 interrelated phenomena; the first relates to the absence of respiratory variation in both phasic and mean venous pressure in the neck and the second to an inspiratory rise in the mean venous pressure.[1,2] The purpose of our study[3] was to ascertain which factors contribute to the latter.

It is perhaps appropriate to review the role of the pericardium in atrial filling. The sudden decrease in pericardial pressure that is associated with early ventricular systolic ejection lowers the pressure around the atria, and consequently increases the gradient from the large thoracic veins to the right atrium.[4] This increase in flow to heart coincides with the right atrial 'x' descent, which, in turn, is due to the displacement of the tricuspid valve away from the atria during ventricular systole, atrial relaxation and, importantly, a fall in the pericardial pressure.[4] Thus, the presence of the pericardial space is an important determinant of atrial filling, especially during inspiration. This space is obliterated in constrictive pericarditis (CP) and consequently the deep 'x' descent so characteristic of tamponade is not seen in CP.

Studies of cardiac tamponade[5] in which the intrapericardial and intrapleural pressures were measured directly have shown little difference in these pressures' respiratory variations. Some observers,[6] however, suggest that the intrapericardial pressure decreases less than the intrapleural pressure with inspiration. During normal inspiration the negative intrathoracic pressure is transmitted to the pericardial space, albeit to a lesser degree, slightly increasing the capacitance of the right atrium, especially during the early part of ventricular systole. Such an increase in capacitance will be associated with "deepening" of the right atrial 'x' descent during inspiration, which would be perceived by the physician as an increase in the variability of the venous pressures in the neck. In severe tamponade the mean right atrial pressure may increase in response to the rise of intraabdominal pressure during slow deep inspiration—the "inspiratory hepatojugular refux phenomenon." [7] This increased rise in pressure accompanied by greater variability (deeper 'x' descent) of the neck vein pressure is somewhat different from the phenomenon seen in CP.[2,3]

In our experience, a similar rise in mean right atrial pressure during slow deep inspiration is usually observed in patients with right-sided heart failure in whom hepatojugular reflux can be demonstrated. Such an increase in mean pressure is usually accompanied by a greater variation in the 'x' and 'y' descents of the venous pressure. Thus, in a strict sense, we suspect that it is only in CP that a rise in venous pressure in the neck during slow deep inspiration is dissociated from an increased variation in phasic pressures, and that it probably is the only condition in which a classical Kussmaul's sign exists.

Because most authors have defined Kussmaul's sign as an increase in venous pressure during inspiration alone and have not characterized it further, a retrospective analysis of published data would not be useful in estimating the sensitivity and specificity of this sign in various conditions.

Theo E. Meyer, FCP(SA)
Oxford, England
Maurice McGregor, MD
Montreal, Canada
12 January 1990

1. Kussmaul A. Ueber schwielige Mediastino-Percarditis und den paradoxen puls. *Berl Klin Wochenschr 1873;10:445–449.*
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CORRECTIONS

The study, "Effect of Combined Administration of Saruplase and Single-Chain Alteplase on Coronary Recanalization in Acute Myocardial Infarction" by Tranchesi et al in the July 15, 1989 issue, on page 230, has 2 errors in Table II. The number of patients in the Group C column is 12, not 2; recanalization at 90 minutes was obtained in 4 patients in the Group A column (which corresponds to 29%, not 23%) and in 4 patients (not 1) in the Group C column.

The study, "Immediate Improvement in Left Ventricular Function After Cardioversion of Atrial Flutter" by Karnegis et al in the November 1, 1989 issue, on page 1045, has a misprint on line 9 in the second column, second paragraph. It should read, "(p <0.025)" instead of "(difference not significant)."

The study, "Metabolic and Functional Effects of Perfluorocarbon Distal Perfusion During Coronary Angioplasty" by Young et al in the April 15, 1990 issue, on page 988, has an error in the second sentence of the last paragraph in the Results section. The sentence should read: "Since distal perfusion essentially controls the variable of flow while the balloon is inflated the relative rates of lactate released during this period can be compared from the great cardiac vein lactate concentrations. Thus, it should not read "oxygen flow" but rather just simply "flow.""

In the study, "Prevention of Late Ventricular Dilatation After Acute Myocardial Infarction by Successful Thrombolytic Reperfusion" by Lavie et al in the July 1, 1990 issue, on page 33, Figures 1 and 2 were inadvertently switched. Figure 1 is Figure 2 and vice versa.

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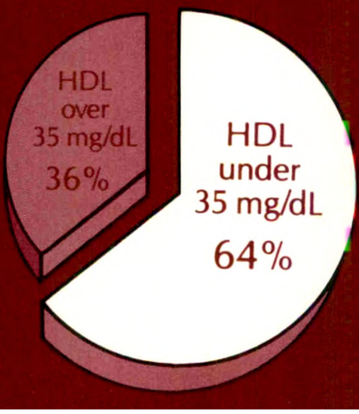

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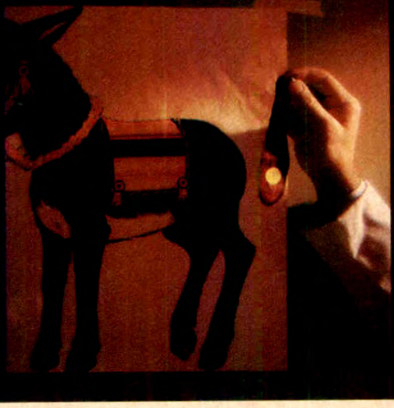

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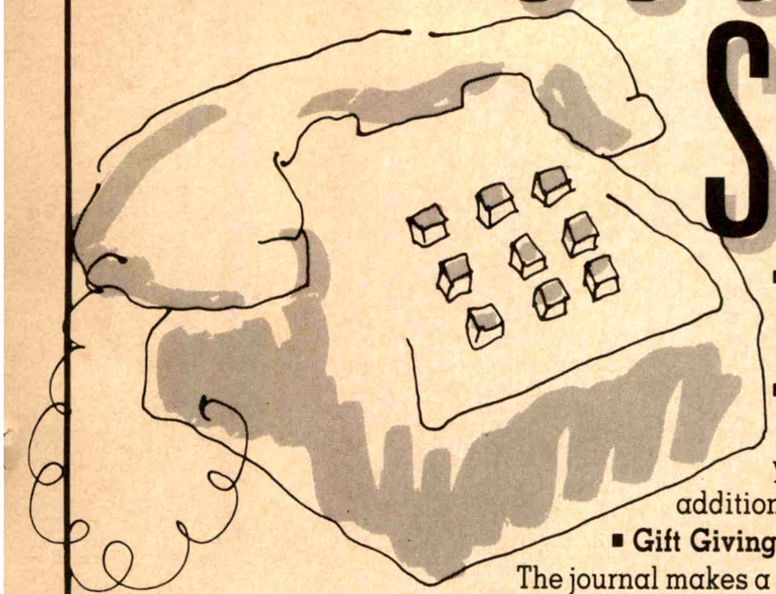

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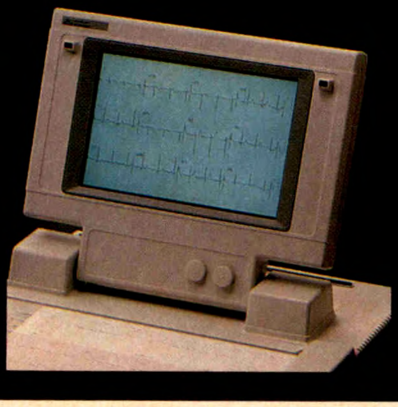

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CORONARY ARTERY DISEASE

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Frequency of Low-Grade Residual Coronary Stenosis After Thrombolysis During Acute Myocardial Infarction
James C. Marshall, Harvey L. Waxman, Anthony Sauerwein, Ian Gilchrist, and Peter B. Kurnik

This study provides demographic and clinical data on 42 patients with low-grade residual stenosis at the infarct lesion after thrombolysis. Events related to infarct narrowing occurred earlier than those not related to infarct narrowing and resulted from both thrombosis and vasospasm.

779

Effect of Verapamil on Mortality and Major Events After Acute Myocardial Infarction (The Danish Verapamil Infarction Trial II—DAVIT II)
The Danish Study Group on Verapamil in Myocardial Infarction*

We studied the effect of verapamil on death and major events in a double-blind, randomized, placebo-controlled multicenter trial. Long-term treatment with verapamil after an acute myocardial infarction caused a significant reduction in major events, and we found a positive effect in patients without heart failure.

786

Impact of Field-Transmitted Electrocardiography on Time to In-Hospital Thrombolytic Therapy in Acute Myocardial Infarction
Labros Karagounis, Steve K. Ipsen, Michael R. Jessop, Kirk M. Gilmore, David A. Valenti, Jeffrey J. Clawson, Sam Teichman, and Jeffrey L. Anderson

The impact of a field-transmitted electrocardiogram was assessed in patients with a possible acute myocardial infarction by tests that were performed in the 6 units of Salt Lake City's emergency rescue system. A total of 71 patients with chest pain suggestive of myocardial ischemia were randomized to in-field ECG (n = 34) or no ECG (n = 37). Our data indicate that in-field ECG may be performed efficiently and may speed the time to in-hospital thrombolytic therapy.

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Sensitivity of a Set of Myocardial Infarction Screening Criteria in Patients with Anatomically Documented Single and Multiple Infarcts
Dorina C. Sevilla, Nancy B. Wagner, William D. Anderson, Raymond E. Ideker, Keith A. Reimer, Eileen M. Mikat, Donald B. Hackel, Ronald H. Selvester, and Galen S. Wagner

A subset of 3 screening criteria has been evaluated to determine their true sensitivities among patients with anatomically documented single and multiple infarctions. The set of screening criteria performed just as well for multiple infarcts as it did for single infarcts. Overall sensitivity of the screening set was 71% in all groups.

796

Two-Year Outcome After Angiographically Documented Myocardial Reperfusion for Acute Coronary Occlusion
David W.M. Muller, Eric J. Topol, Barry S. George, Dean J. Kereiakes, Lynn G. Aronson, Kerry L. Lee, Charles W. Abbottsmith, Stephen G. Ellis, Robert M. Califf, and the TAMI Study Group

A cohort of 810 patients, the majority of whom underwent urgent or elective mechanical revascularization after intravenous thrombolytic therapy, was followed after hospital discharge for a mean period of 18.8 months. All-cause mortality was 3.3%, nonfatal reinfarction occurred in 5.1%, and patients who survived tended to be younger, to have better left ventricular function and to have less extensive coronary artery disease. A strategy of intravenous thrombolysis combined, when appropriate, with predischarge mechanical revascularization is associated with an excellent long-term prognosis.

802

Functional Significance of Myocardial Perfusion Defects Induced by Dipyridamole Using Thallium-201 Single-Photon Emission Computed Tomography and Two-Dimensional Echocardiography
Avanindra Jain, Jose Suarez, John J. Mahmarian, William A. Zoghbi, Miguel A. Quinones, and Mario S. Verani

We evaluated the mechanism of myocardial perfusion defects in 27 patients who underwent thallium-201 single-photon emission computed tomography after dipyridamole. Most thallium-201 defects are associated with transient wall motion abnormalities indicative of myocardial ischemia. Because myocardial oxygen demand did not change significantly, myocardial ischemia in these patients is likely to be due to diminished regional blood flow related to a "subendocardial steal" induced by dipyridamole.

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Left Ventricular Dilatation and Pulmonary Thallium Uptake After Single-Photon Emission Computed Tomography Using Thallium-201 During Adenosine-Induced Coronary Hyperemia
Abdulmassih S. Iskandrian, Jaekyeong Heo, Thach Nguyen, Edward Lyons, and Elizabeth Paugh

The purpose of this study was to examine the implications of left ventricular dilatation and increased pulmonary thallium uptake during adenosine-induced coronary hyperemia. We found that adenosine-induced coronary hyperemia may cause LV dilatation and increased lung thallium uptake on the basis of subendocardial ischemia.

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Effects of Bepridil and Diltiazem on Ventricular Repolarization in Angina Pectoris

Christian Funck-Brentano, Philippe Coudray, Juan Planellas, Gilbert Motté, and Patrice Jaillon

In a double-blind, randomized multicenter study performed in patients with stable angina pectoris, we analyzed the time course and predictors of the effects of bepridil on QT and QTc intervals. Bepridil tended to produce more absolute QTc prolongation in patients with a short QTc interval or a slow heart rate at baseline compared to patients with a comparatively long QTc interval or a rapid heart rate.

818

Effects of Intravenous Verapamil on Left Ventricular Relaxation and Filling in Stable Angina Pectoris

Sandro Betocchi, Federico Piscione, Pasquale Perrone-Filardi, Leonardo Pace, Maurizio Cappelli-Bigazzi, Bruno Alfano, Andrea Ciarmiello, Marco Salvatore, Mario Condorelli, and Massimo Chiariello

We studied 12 patients with coronary artery disease, undergoing right- and left-sided cardiac catheterization as well as simultaneous radionuclide angiography, before and during intravenous administration of verapamil. Intravenous verapamil administration in patients with CAD led to an improvement in both left ventricular isovolumic relaxation and early filling, through its direct action on myocardium and changes in the loading conditions.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

826

Analysis of Programmed Stimulation Methods in the Evaluation of Ventricular Arrhythmias in Patients 20 Years Old and Younger

Michael J. Silka, Jack Kron, Joel E. Cutler, and John H. McAnulty

The purpose of this study was to evaluate the responses to programmed ventricular stimulation in young patients undergoing electrophysiologic testing. Our data indicated the following: aggressive stimulation protocols appear to be required for induction of sustained ventricular tachycardia in most young patients; nonsustained polymorphic VT, as a response to aggressive programmed stimulation, is of uncertain significance; and that coupling intervals ≤190 ms may correlate with the induction of VF.

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Long-Term Follow-Up in Patients with Incessant Ventricular Tachycardia

Robert J. Hariman, Dayi Hu, Jose L. Gallastegui, Karen J. Beckman, and Jerry L. Bauman

We studied 17 patients with coronary artery disease, idiopathic dilated cardiomyopathy or no organic heart disease who presented with incessant ventricular tachycardia. Nine of these patients with incessant VT had remission over a mean follow-up of 55 ± 34 months after discontinuation of antiarrhythmic drugs. The probability of remission in patients surviving incessant VT warrants trials of discontinuation of such drugs.

837

The Nuclear Pacemaker: Is Renewed Interest Warranted?

Victor Parsonnet, Alan D. Bernstein, and Gershon Y. Perry

From 1973 through 1987, we implanted 155 radioisotope-powered "nuclear" pacemakers in 132 patients. In following these patients, we found that nuclear pacemakers are safe and reliable and that their initial cost appears to be offset by their longevity and the resulting decrease in the frequency of reoperations. It is reasonable to suggest that further use be made of long-lasting nuclear power sources for modern pacemakers and other implantable rhythm-management devices.

CONGESTIVE HEART FAILURE

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Effects of Metoprolol on Rest and Exercise Cardiac Function and Plasma Catecholamines in Chronic Congestive Heart Failure Secondary to Ischemic or Idiopathic Cardiomyopathy

John W. Nemanich, Richard C. Veith, Itamar B. Abrass, and John R. Stratton

Ten patients with chronic congestive heart failure were given metoprolol to examine its effect on cardiac function, aerobic capacity and sympathetic nervous system activity. Improvements occurred in both rest and exercise ventricular performance and in aerobic capacity, and were associated with a decline in resting sympathetic nervous system activity.

VALVULAR HEART DISEASE

849

Digital Acoustical Analysis of Normal and Bimodal Björk-Shiley 60° Convexo-Concave Heart Valves

Gerald A. Kien, Bradley Jeffries, Hart V. Katz, Bruce A. Herman, Ronald F. Carey, Daniel J. Chwirut, and Harry F. Bushar

Fracture of the outlet strut of the Björk-Shiley 60° convexo-concave valve has been attributed to a bimodal closing pattern in certain valves in which the closing disk rotates about the inlet strut, causing upward displacement of the outlet strut and its eventual fracture. We reported the in vivo studies of the normal BS60CC valve and the in vitro studies of the normal and bimodal BS60CC valves using a digital acoustical signal processing technique in which the individual collisions (the impact history) of the occluder disk with the valve body are revealed. The bimodal valves showed values significantly greater than those observed in the normal in vitro valve group and in the normal patient population ($p < 0.0001$).

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William C. Roberts

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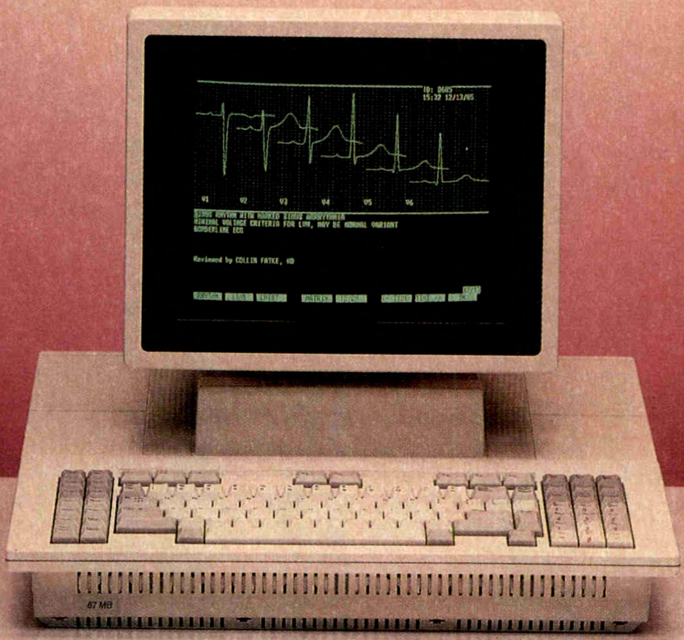
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SINUS RHYTHM WITH MARKED SINUS ARRHYTHMIA
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CORONARY ARTERY DISEASE

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Frequency of Low-Grade Residual Coronary Stenosis After Thrombolysis During Acute Myocardial Infarction

James C. Marshall, Harvey L. Waxman, Anthony Sauerwein, Ian Gilchrist, and Peter B. Kurnik

The demographic, clinical and angiographic characteristics of 42 patients with low-grade (<50%) infarct lesion residual diameter stenosis after thrombolysis were retrospectively assessed and correlated with clinical outcome. The group comprised 21% of a postthrombolysis population and experienced frequent readmission and coronary arteriography for chest pain. Postinfarction clinical events related to the infarct lesion occurred early in follow-up and resulted from both thrombosis and vasospasm.

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Effect of Verapamil on Mortality and Major Events After Acute Myocardial Infarction (The Danish Verapamil Infarction Trial II-DAVIT II)

The Danish Study Group on Verapamil in Myocardial Infarction*

The DAVIT II study demonstrated a beneficial effect of treatment with verapamil, 120 mg 3 times daily, from the second week after an acute myocardial infarction and the following 18 months. Eighteen-month major event rate (i.e., reinfarction or death) and cardiac event rate (i.e., reinfarction or cardiac death) were significantly reduced in the verapamil-treated patients compared with the placebo-treated patients. The effect was most pronounced in patients without heart failure.

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Impact of Field-Transmitted Electrocardiography on Time to In-Hospital Thrombolytic Therapy in Acute Myocardial Infarction

Labros Karagounis, Steve K. Ipsen, Michael R. Jessop, Kirk M. Gilmore, David A. Valenti, Jeffrey J. Clawson, Sam Teichman, and Jeffrey L. Anderson

The impact of a field-transmitted electrocardiogram (ECG) was assessed in patients with a possible acute myocardial infarction (AMI) by tests that were performed in the 6 units of Salt Lake City's emergency rescue system. A total of 71 patients with chest pain suggestive of myocardial ischemia were randomized to in-field ECG (n = 34) or no ECG (n = 37).

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Time on-scene was similar in both groups (16 minutes). Similarly, time of transport averaged 18 minutes in each group. On hospital arrival, 6 patients with AMI were able to receive thrombolytic therapy after 48 ± 12 minutes, compared with 103 ± 44 minutes for 51 historical control patients ($p < 0.01$) and 68 ± 29 minutes for 6 concurrent control patients without in-field ECG. Our data indicate that in-field ECG may be performed efficiently and may speed the time to in-hospital thrombolytic therapy.

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Sensitivity of a Set of Myocardial Infarction Screening Criteria in Patients with Anatomically Documented Single and Multiple Infarcts

Dorina C. Sevilla, Nancy B. Wagner, William D. Anderson,
Raymond E. Ideker, Keith A. Reimer, Eileen M. Mikat, Donald B. Hackel,
Ronald H. Selvester, and Galen S. Wagner

A subset of 3 screening criteria (Q wave ≥30 ms in aVF, any Q or R wave ≤10 ms and ≤0.1 mV in V_2, and R wave ≥40 ms in V_1) has been evaluated to determine their true sensitivities among patients with anatomically documented single ($n = 71$) and multiple ($n = 32$) infarctions. In the single inferior infarct group, the aVF criterion alone was 83% sensitive, and 90% sensitive when combined with other criteria. The V_2 criterion was 67% sensitive in the single anterior infarct group. No single criterion proved sensitive in identifying a posterolateral infarct. This set of screening criteria performed just as well for multiple infarctions, with a 72% cumulative sensitivity. The overall sensitivity of the screening set in the 103 patients was 71%.

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Two-Year Outcome After Angiographically Documented Myocardial Reperfusion for Acute Coronary Occlusion

David W.M. Muller, Eric J. Topol, Barry S. George, Dean J. Kereiakes,
Lynn G. Aronson, Kerry L. Lee, Charles W. Abbottsmith, Stephen G. Ellis,
Robert M. Califf, and the TAMI Study Group

A cohort of 810 patients discharged from hospital alive after reperfusion therapy for acute myocardial infarction was followed for a mean period of 18.8 months. After intravenous thrombolytic therapy, the majority underwent urgent or elective mechanical revascularization using coronary angioplasty (62%) or coronary artery bypass graft surgery (21%) before hospital discharge. During the follow-up period, all-cause mortality was 3.3% and nonfatal reinfarction occurred in 5.1%. Patients who survived tended to be younger, to have better left ventricular function and to have less extensive coronary artery disease. These data suggest that a strategy of intravenous thrombolysis combined, when appropriate, with predischarge mechanical revascularization is associated with an excellent long-term prognosis.

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Functional Significance of Myocardial Perfusion Defects Induced by Dipyridamole Using Thallium-201 Single-Photon Emission Computed Tomography and Two-Dimensional Echocardiography

Avanindra Jain, Jose Suarez, John J. Mahmarian, William A. Zoghbi, Miguel A. Quinones, and Mario S. Verani

The mechanism of myocardial perfusion defects in 27 patients with coronary artery disease who underwent thallium-201 single-photon emission computed tomography (SPECT) was evaluated. SPECT images were acquired 50 minutes and 4 hours after oral dipyridamole administration. Two-dimensional echocardiograms were obtained concomitantly with SPECT for assessing regional wall motion function. Thallium-201 perfusion defects were observed in 20 of 27 patients (74%), and underwent complete or partial filling-in in 16 cases. Fourteen of these patients (87.5%) had evidence of transient ischemia during dipyridamole, as evidenced by new wall motion abnormality or worsening of preexisting abnormality by 2-dimensional echocardiography. Ten of 11 patients (91%) with normal perfusion or fixed defects by SPECT had no further deterioration in wall motion after dipyridamole and hence were considered to have no evidence of ischemia. Thus, the majority of transient thallium-201 perfusion defects after dipyridamole are associated with transient wall motion abnormalities indicative of myocardial ischemia.

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Left Ventricular Dilatation and Pulmonary Thallium Uptake After Single-Photon Emission Computed Tomography Using Thallium-201 During Adenosine-Induced Coronary Hyperemia

Abdulmassih S. Iskandrian, Jaekyeong Heo, Thach Nguyen, Edward Lyons, and Elizabeth Paugh

This study examined the implications of left ventricular (LV) dilatation and increased pulmonary thallium uptake during adenosine-induced coronary hyperemia. The lung-to-heart thallium ratio was significantly higher in patients with coronary artery disease (CAD) ($n = 52$) than in normal subjects ($n = 7$). There was a significant correlation between the perfusion abnormality and the lung-to-heart thallium ratio. The LV dilatation was mostly due to an increase in cavity dimension and was seen in patients with CAD but not in normal subjects. These changes correlated with the severity of the perfusion abnormality. Thus, adenosine-induced coronary hyperemia may cause LV dilatation and increased lung-thallium uptake on the basis of subendocardial ischemia.

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Effects of Bepridil and Diltiazem on Ventricular Repolarization in Angina Pectoris

Christian Funck-Brentano, Philippe Coudray, Juan Planellas, Gilbert Motté, and Patrice Jaillon

In a double-blind, randomized multicenter study performed in patients with stable angina pectoris, we analyzed the time course and predictors of the effects of bepridil (300 to 500 mg/day; $n = 45$) and diltiazem (180 to

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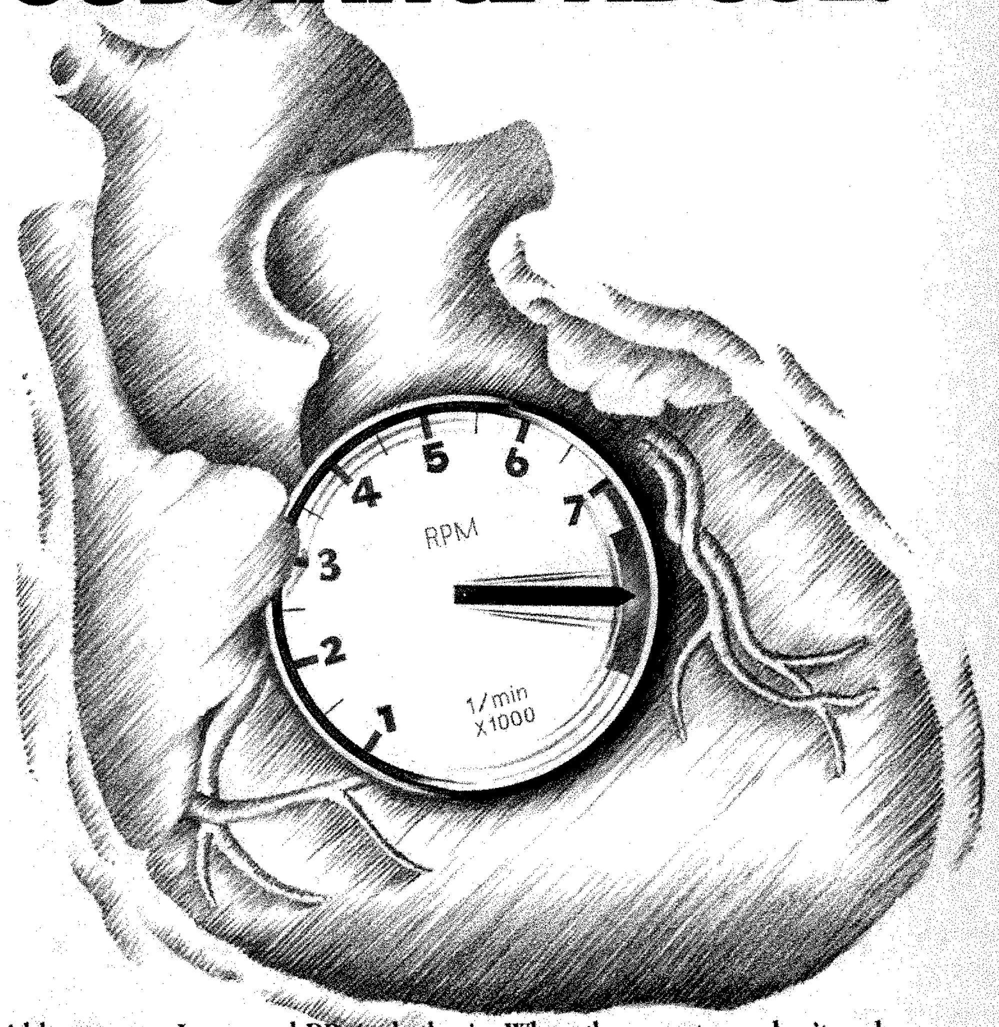
BEYOND THE SYMPTOMS MAY BE SUBSTANCE ABUSE.



Rapid heart rate. Increased BP. Arrhythmia. When the symptoms don't make sense... the reason may be substance abuse.

Even "occasional" use of cocaine can cause a wide range of physiological and psychological symptoms that may mimic systemic disease. Even more frightening is the fact that cocaine can cause sudden death, regardless of the dose, blood levels, or route of administration.

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For information, healthcare professionals may call the National Clearinghouse for Alcohol and Drug Abuse: 1-301-468-2600, Monday through Friday, 8:30 AM–4:30 PM EST.

HELP STOP SUBSTANCE ABUSE.
ASK THE QUESTIONS.
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300 mg/day; n = 42) on QT and QTc intervals. After randomization and a baseline electrocardiographic recording, patients were seen at 4 follow-up visits: 14, 28, 78 and 112 days after treatment was begun. Bepridil, but not diltiazem, prolonged QT and QTc intervals. The majority of patients treated with bepridil did not develop marked QTc prolongation. On average, the steady-state effects of bepridil on QTc interval duration were observed on an electrocardiogram recorded after 14 days of treatment. However, individual variability indicated that subsequent electrocardiographic recordings might be required in a given patient. Bepridil tended to produce more absolute QTc prolongation in patients with a short QTc interval or a slow heart rate at baseline compared to patients with a comparatively long QTc interval or a rapid heart rate.

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Effects of Intravenous Verapamil on Left Ventricular Relaxation and Filling in Stable Angina Pectoris

Sandro Betocchi, Federico Piscione, Pasquale Perrone-Filardi, Leonardo Pace, Maurizio Cappelli-Bigazzi, Bruno Alfano, Andrea Ciarmiello, Marco Salvatore, Mario Condorelli, and Massimo Chiariello

We studied 12 patients with coronary artery disease (CAD), undergoing right- and left-sided cardiac catheterization as well as simultaneous radionuclide angiography, before and during intravenous administration of verapamil. The heart rate was kept constant by atrial pacing in both studies. Left ventricular (LV) pressure-volume relations were obtained. Verapamil decreased LV systolic pressure and the end-systolic pressure/volume ratio and increased LV end-diastolic and pulmonary capillary pressures as well as cardiac index. The time constant of isovolumic relaxation shortened and peak filling rate increased. Late diastolic filling was not affected by verapamil. Thus, intravenous verapamil administration in patients with CAD led to an improvement in both LV isovolumic relaxation and early filling, through its direct action on myocardium and changes in the loading conditions.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Analysis of Programmed Stimulation Methods in the Evaluation of Ventricular Arrhythmias in Patients 20 Years Old and Younger

Michael J. Silka, Jack Kron, Joel E. Cutler, and John H. McAnulty

This study evaluates the responses to programmed ventricular stimulation in young patients undergoing electrophysiologic testing. A defined, stepwise protocol was applied in 55 consecutive patients, both with and without clinical ventricular arrhythmias. Of 17 patients with documented sustained VT, 12 (71%) had induction of the arrhythmia. The sensitivity of programmed ventricular stimulation was significantly enhanced by the use of 3 and 4 extrastimuli ($p = 0.02$). Ventricular fibrillation was induced in 5 patients, each as a response to extrastimuli coupling intervals ≤ 190 ms. Nonsustained polymorphic ventricular tachycardia was also frequent-

Continued on page A30

ACTIVASE®

ALTEPLASE, RECOMBINANT

A TISSUE PLASMINOGEN ACTIVATOR

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

ACTIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) ($p = 0.26$).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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both reduced. Mean ejection fraction increased from 0.15 ± 0.06 to 0.25 ± 0.11, and 6 of 8 subjects had $\geq$6 point increases. Both resting plasma norepinephrine and epinephrine were reduced, whereas circulating lymphocyte β-adrenergic receptor numbers were unchanged. Thus, metoprolol therapy was associated with an improvement in both rest and exercise ventricular performance and improved maximal aerobic capacity. These improvements were associated with a decrease in resting sympathetic nervous system activity.

VALVULAR HEART DISEASE

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Digital Acoustical Analysis of Normal and Bimodal Björk-Shiley 60° Convexo-Concave Heart Valves

Gerald A. Kien, Bradley Jeffries, Hart V. Katz, Bruce A. Herman, Ronald F. Carey, Daniel J. Chwirut, and Harry F. Bushar

Fracture of the outlet strut of the Björk-Shiley 60° convexo-concave (BS60CC) valve has been attributed to a bimodal closing pattern in certain valves in which the closing disk rotates about the inlet strut, causing upward displacement of the outlet strut and its eventual fracture. This article reports the in vivo studies of the normal BS60CC valve and the in vitro studies of the normal and bimodal BS60CC valves using a digital acoustical signal processing technique in which the individual collisions (the impact history) of the occluder disk with the valve body are revealed. In vitro analysis of the closing acoustical signals of normal BS60CC valves showed impact history cluster width means not significantly different than those observed in clinically normal patients with BS60CC valves ($p > 0.1$). The bimodal valves showed values significantly greater than those observed in the normal in vitro valve group and in the normal patient population ($p < 0.0001$).

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OCTOBER 1, 1990, VOL. 66, NO. 10

Frequency of Low-Grade Residual Coronary Stenosis After Thrombolysis During Acute Myocardial Infarction

James C. Marshall, DO, Harvey L. Waxman, MD, Anthony Sauerwein, MD,
Ian Gilchrist, MD, and Peter B. Kurnik, MD

The clinical, angiographic and demographic characteristics of 42 patients with low-grade ($<50\%$) residual stenosis at the infarct lesion after thrombolysis for acute myocardial infarction (MI) were assessed. The study group (group I) represented 21% of 198 consecutive patients receiving thrombolytic therapy over a 59-month period. Data on the 156 remaining patients were pooled for comparison (group II). Group I patients were predominantly men (86%) who were cigarette smokers (81%). Group II patients were predominantly men (75%, $p > 0.10$) but were significantly older (52 ± 12 vs 56 ± 10 years, $p = 0.02$). Prior acute MI or angina was unusual in group I. Sixty percent had no significant ($>50\%$) residual coronary artery disease while 25% had residual single artery disease. Average significant ($>50\%$ diameter stenosis) residual vessel disease was 0.6 ± 1.0 for group I and 1.9 ± 0.9 for group II ($p < 0.001$). In group I, average residual infarct lesion diameter stenosis was 36 ± 7% in the right anterior oblique and 34 ± 8% in the left anterior oblique views. Thirty-nine group I patients were discharged with medical therapy and 100% follow-up was obtained over a mean interval of 18 ± 17 months. Fifteen patients experienced chest pain after acute MI accounting for 17 discrete events. Fifty-nine percent of group I had a benign course on follow-up. Eight events were classified as unstable angina, 4 as acute MI and 5 as atypical angina. Documented coronary vasospasm occurred in 3. The infarct narrowing accounted for 58% of documented ischemia and 41% of symptomatic events. Antiplatelet agents, warfarin and residual lesion morphology did not clearly influence frequency of events, whereas data regarding cigarette smoking were suggestive ($p = 0.06$). Events clearly associated with the infarct narrowing occurred earlier (4 ± 4 months) than events not related to (23 ± 15 months, $p < 0.01$). Ischemic events unrelated to the infarct lesion were often related to progressive stenosis or occlusion at the site of previously nonsignificant disease.

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The natural history and response to treatment of patients with infarct lesion residual diameter stenosis $<50\%$ after thrombolytic therapy for acute myocardial infarction (MI) are unknown. Most acute MIs are related to thrombotic occlusion at the site of an atherosclerotic plaque.[1] Recent published reports on thrombolysis have suggested that while a critical ($\geq 70\%$) diameter stenosis is usually present before occlusion, the incidence of noncritical stenosis is not uncommon and approximates 10 to 20% of all patients undergoing thrombolysis.[2-5] Information concerning nonsignificant ($<50\%$) "low grade" stenoses after thrombolysis including follow-up and response to treatment is unavailable.[6] This study provides demographic and clinical data on a population of acute MI patients who received thrombolytic therapy and underwent early arteriography, and were found to have low-grade infarct lesion residual diameter stenosis.

METHODS

Patients: One hundred ninety-eight consecutive patients admitted with a diagnosis of acute MI and receiving conventional doses of thrombolytic therapy over a 59-month period (February 1984 to January 1989) were identified. All patients had routine therapy (heparin) after acute MI and had coronary arteriography. Cineangiographic films were reviewed and all lesions assessed by digital caliper measurement when the infarct-related artery had greatest residual diameter stenosis of $\leq 70\%$ by visual estimate. Acute MI was diagnosed by conventional criteria including prolonged chest pain and ST elevation ≥ 0.1 mV in 2 contiguous leads, or Q-wave evolution, or both. Diagnostic creatinine kinase-MB isoenzyme pattern was present in all patients. Demographic and angiographic information was obtained for all

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TABLE I Comparative Data of Groups I and II

	Group I (n = 42)	Group II (n = 156)	p Value
Demographic			
Mean age (years)	52 ± 12	56 ± 10	0.02
% Men	86	75	NS
Thrombolytic treatment			
Intracoronary streptokinase (%)	9 (21)	43 (28)	NS
Intravenous streptokinase (%)	5 (12)	8 (5)	NS
Intravenous tissue plasminogen activator (%)	28 (67)	105 (67)	NS
Infarct artery (%)			
Right	19 (45)	65 (42)	NS
Left anterior descending	16 (38)	64 (41)	NS
Circumflex	7 (17)	23 (15)	NS
Saphenous vein graft	0 (0)	4 (2)	NS
Number of vessels narrowed >50%	0.6 ± 1.0	1.9 ± 0.9	0.001
Ejection fraction (%)	56 ± 14	52 ± 12	NS

NS = not significant.

patients undergoing thrombolysis from the angiographic data registry. In patients found to have residual infarct narrowing $\leq 50\%$ (group I), clinical data were obtained by chart review and by patient interview. Those with significant infarct narrowing ($>50\%$) were designated group II.

Identification of the infarct-related lesion: Coronary arteriography was performed using the standard Judkins technique and catheters in all cases. Ventriculography was performed using standard technique in right and/or left oblique views. The infarct narrowing was identified anatomically in patients undergoing acute arteriography by the presence of 100% thrombotic occlusion that later reperfused, the most critical residual stenosis in the infarct-related artery after thrombolysis, or intraluminal thrombus in the region of the most severe atherosclerotic narrowing in a known infarct artery. The anatomic location of the infarct lesion was consistent with infarct location as determined by electrocardiography as well as by wall motion abnormalities on ventriculography. In patients having nonacute arteriography before discharge, the infarct lesion was then identified as that having the greatest diameter stenosis in the infarct artery. Stenosis of $>50\%$ by visual estimate was considered significant in noninfarct arteries.

Measurements of infarct narrowing were obtained using a digital caliper as previously described and validated.[7-9] Measurements were obtained in 2 orthogonal views by 2 independent observers using a standard cineangiographic projector (Vanguard Inc.). A cine frame in diastole was selected from each view to allow the clearest delineation of the lesion edges and most severe diameter stenosis for caliper measurement (Mitumoyo, Fowler Inc.) Lesion morphology was defined according to the criteria of Ambrose et al[10] and coronary flow was assessed using the Thrombolysis in Myocardial Infarction trial classification.[11]

The normal vessel diameter was defined in an angiographically normal arterial segment both proximal and distal to the infarct narrowing before any branching occurred. These measurements were made as close to the infarct lesion as possible and their average was then taken as the normal vessel diameter. Segments having diffuse disease were excluded from analysis of the normal diameter. Percent diameter stenosis was calculated using the difference of the normal diameter and the residual lumen diameter divided by the normal diameter and the quotient multiplied by 100. A value $\leq 50\%$ was required in 2 orthogonal views for group I inclusion.

To measure intraobserver and interobserver variability, a series of 3 caliper measurements were performed on the infarct lesion by 2 independent observers where the lesion location was mutually agreed on (40 of 42 patients). For interobserver variability, linear regression demonstrated an r value of 0.9. For intraobserver variability, the standard deviations (in percent diameter stenosis) from each series of 3 measurements were averaged and this value was 2.4 (range 0.5 to 5.7), providing an acceptable level of variability.[7-9]

Data collection: Group I clinical data were subject to the following definitions: Family history was defined as acute MI at age ≤ 55 years in a first-degree relative. Tobacco use required smoking >10 cigarettes per day. Cocaine use implied utilization within 24 hours of acute MI. Hypercholesterolemia was defined as acute MI admission serum total cholesterol ≥ 250 mg/dl. The medication usage must have been present within 1 month of acute MI. Data concerning patient age, gender, infarct-related artery, extent of coronary artery disease, type and route of thrombolytic therapy and ejection fraction were obtained from the angiography registry for both group I and II patients.

Follow-up: Follow-up concerned only group I patients and was obtained by office visit or direct telephone interview as well as referring physician contact for 100% of study patients. Clinical end points terminating further follow-up included aortocoronary bypass, percutaneous transluminal coronary angioplasty of the infarct narrowing, demonstration of total occlusion of the infarct narrowing and death. Information obtained in the follow-up period included: mortality, cardiac symptoms including typical or atypical angina and dyspnea, activity level, current medical regimen, reassessment of risk factors for coronary artery disease, subsequent hospitalizations and repeat coronary arteriography or exercise testing. Repeat angiography was reviewed in all cases and caliper measurements performed. Hospitalization data were reviewed when repeat angiography or a question of recurrent ischemia existed. A repeat event was defined as chest pain requiring readmission, sudden death or congestive heart failure.

Statistics: The chi-square, Student's *t*, Fisher's exact and log-rank tests were used. Data are expressed as mean ± standard deviation. A p value <0.05 was considered statistically significant.

RESULTS

Demography: Forty-two of 198 (21%) patients were identified as having an infarct narrowing $\leq 50\%$ and constitute group I. The remaining 156 patients had significant ($>50\%$) residual diameter stenosis and constitute group II. Average age was 52 ± 12 years in group I and 56 ± 10 ($p = 0.02$) in group II. Risk factors in group I included tobacco in 34 (81%), family history in 19 (45%), hypercholesterolemia in 13 (31%), hypertension in 10 (24%), diabetes in 5 (12%), migraines in 3 (7%), prior acute MI in 1 (2%), birth control pill use in 1 (2%) and cocaine use in 1 (2%). Comparative data for groups I and II are listed in Table I.

Clinical characteristics: Prior to acute MI, antecedent angina occurred in 19 (45%) group I patients. The use of antiplatelet (4 patients, 10%) or antianginal (1 patient, 2%) agents was infrequent.

Thrombolysis and postmyocardial infarction angiography: All group I patients had a clinical and angiographic response to thrombolysis as defined by diminution in chest pain, improvement in electrocardiographic injury current and a patent infarct artery. The average time to thrombolysis was 2.1 ± 1.1 hours and angiography 5.4 ± 7.3 days. Infarct narrowing residual diameter stenosis (average of 3 measurements from 2 observers) was 36 ± 7 and 34 ± 8% in the right and left oblique views, respectively. No other significant coronary artery disease was found in 25 (60%). Residual single artery disease ($>$50% stenosis) was found in 11 (25%), double artery disease in 2 (5%) and 3-artery or left main disease, or both, in 4 (10%). Comparative data are listed in Table I. For group II, residual single artery disease was present in 63 (40%), double artery in 42 (27%) and 3-artery or left main disease in 51 (33%).

Twenty-two group I patients underwent acute angiography and all had definite identification of the infarct narrowing based on the aforementioned criteria. Eighteen group I patients with only nonacute coronary arteriography had a high probability of infarct narrowing identification. Two group I patients had minimal or no atherosclerosis and therefore the infarct narrowing remained uncertain, although the infarct-related artery was known with high probability in both cases.

Several patients with $\geq$50% diameter stenosis on acute angiography had $<$50% diameter stenosis on subsequent predischarge follow-up angiography. This is a well-documented phenomenon.[2,4,12] Follow-up angiograms were used to determine infarct lesion diameter stenosis. Gross lesion morphology was evaluated for group I and consisted of type I narrowing (smooth eccentric) in 12 patients (29%), type II (irregular eccentric) in 17 (41%), concentric irregular narrowing in 8 (19%), concentric smooth narrowing in 1 (2%), minimal irregularities or normal coronary arteries in 2 (5%), minimal irregularity with thrombus in 1 (2%) and thrombus only in 1 (2%). Three patients (7%) had collaterals to the infarct artery during acute arteriography, with resolution on later arteriography (when infarct narrowing was $\leq$50%) in all but 1 who had distal embolization. Flow grade from the Thrombolysis in Myocardial Infarction study was normalized (III) in all patients as seen on the cineangiogram from which caliper measurements were derived. Mean time to angiography differed for those with complex (types I and II) versus those without (7 ± 8 vs 4 ± 6 days) complex lesions, but not significantly ($p > 0.10$).

In testing for significant differences in the frequency of low-grade residual stenosis for anatomic site, type and route of thrombolysis, no statistically significant result was evident.

Noninvasive data: Admission and discharge electrocardiograms were reviewed for all group I patients. Thirty-four patients had Q-wave acute MI (81%) and 8 had non-Q-wave acute MI (19%). Fifteen patients had anterior (36%), 23 had inferior or inferoposterior (55%) and 4 had lateral or posterolateral acute MI (9%) by electrocardiogram.

Twenty-eight of 33 patients (85%) had no reperfusion or electrocardiographic change (when no thallium

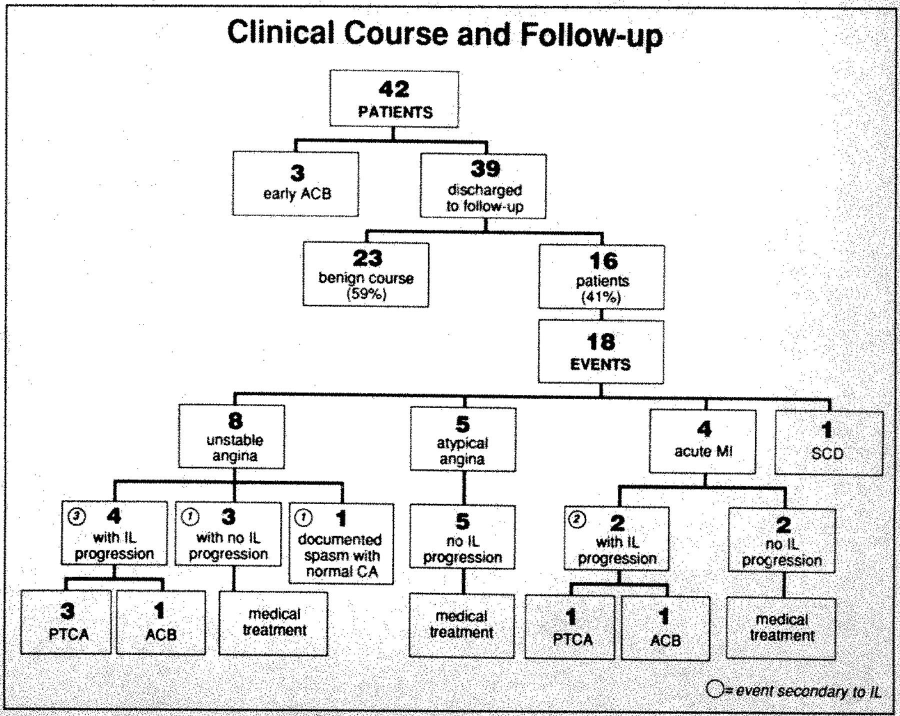

FIGURE 1. Flow chart demonstrating clinical and angiographic outcome of patients having repeat events after infarction. ACB = aortocoronary bypass; CA = coronary arteries; IL = infarct lesion; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SCD = sudden cardiac death; O = proportion having event secondary to infarct lesion.

data were available) consistent with ischemia on their postinfarction treadmill study, whereas 5 patients had a scan suggesting ischemia.

Postinfarction clinical events: During acute MI, 5 group I patients (12%) had primary ventricular fibrillation before the administration of thrombolytic therapy and were successfully resuscitated. Three patients underwent early bypass surgery and were excluded from follow-up.

One patient had in-hospital angina after acute MI. There were no in-hospital deaths or episodes of congestive heart failure. Thirty-nine patients were discharged from the hospital on medical therapy. The mean follow-up period was 18 ± 17 months. No patient had follow-up of <6 months.

Medical therapy included antiplatelet or anticoagulant therapy in 38 of 39 (95%), nitrates in 28 of 40 (70%), calcium channel blocking therapy in 31 of 40 (78%) and β blockers in 13 of 40 (33%) patients. Twelve patients were discharged on warfarin with 4 taking dipyridamole or aspirin concomitantly.

Mortality over the follow-up period was low, with 1 of 39 patients (3%) dying from apparent cardiovascular cause (sudden death). Over the course of follow-up, 16 of 39 patients (41%) had events, with 15 experiencing chest pain (Figure 1). Among the 15 patients with chest pain, 16 discrete events necessitated readmission and coronary angiography, whereas 1 patient had angina after catheterization. The 17 events were classified clinically as unstable angina in 8, atypical angina in 5 and acute MI in 4. Twenty-three patients (59%) had a benign course over the follow-up period as defined by the absence of reported symptoms.

Repeat coronary angiography: All 14 patients readmitted for chest pain underwent coronary angiography. With use of the information obtained from angiography in addition to clinical and electrocardiographic data, an assessment was made regarding the involvement of the prior infarct narrowing in the new clinical syndrome. This was based on the presence of progression in infarct narrowing diameter stenosis to critical range (≥70%), new ST changes in the leads denoting prior infarction due to the original infarct narrowing and the presence of a clinical syndrome compatible with angina pectoris or acute MI.

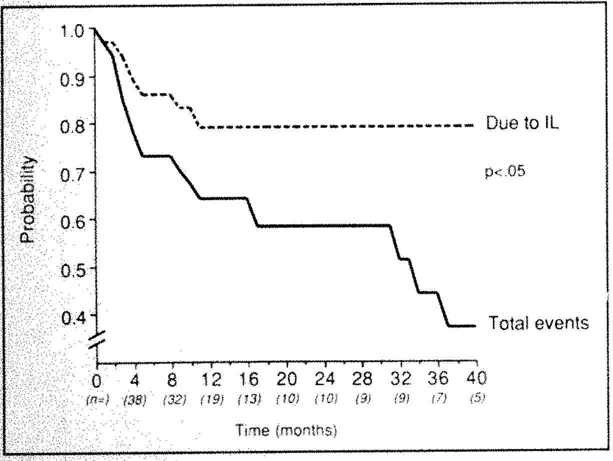

FIGURE 2. Life table plot comparing freedom from total cardiac events to events secondary to the infarct lesion. Clinical activity attributable to the infarct lesion occurs early. IL = infarct lesion.

Four of 8 patients with unstable angina were found to have progression of their prior nonsignificant infarct narrowing to the critical range, and that combined with electrocardiographic and clinical data suggested a relation to the new clinical syndrome in 3 of the 4 patients. These 3 patients had subsequent percutaneous transluminal coronary angioplasty (see Figure 1) and clinical improvement. The fourth patient with unstable angina and infarct-narrowing progression had new critical stenosis in a region remote from the infarct artery as suggested by new electrocardiographic changes. Three patients had no progression and were given medical therapy. Three patients with unstable angina (1 with progression, 2 without) had a syndrome consistent with active coronary vasospasm at or near the previous infarct narrowing as documented by angina with ST elevation, response to nitroglycerin or nifedipine, and absence of thrombosis or occlusion on the coronary arteriogram.

Five patients with atypical chest pain underwent repeat coronary angiography. All received medical therapy after no progression was found. The subsequent follow-up course remained benign for 4 of the 5 patients over a mean interval of 18 ± 17 months, although 1 patient had acute MI secondary to infarct narrowing occlusion 8 months after the index acute MI.

Four patients had acute MI and the data permitted clear identification of a former nonsignificant infarct narrowing as the culprit lesion in the new acute MI in 2. The other 2 events were related to previously documented noncritical stenoses in arteries differing from the original infarct vessel.

Therefore, 6 of 15 patients (40%) with cardiac events had progression of their prior nonsignificant infarct lesion. Vasospasm and progression at the infarct narrowing accounted for 7 of 17 total events (41%) and 7 of 12 documented ischemic events (58%). One patient who died suddenly did not have postmortem examination. Regarding the time course of events, the mean time to event in the 16 patients was 9 ± 11 months. Mean time to the repeat cardiac event was 4 ± 4 months in 7 patients with symptomatic progression or active spasm at the infarct narrowing. Mean time to event was 23 ± 15 months ($p < 0.01$) in patients with ischemic events distant from the infarct narrowing. The probability of remaining free from any event (including atypical angina) is plotted with the probability of remaining free from infarct lesion ischemia in Figure 2.

Risk factors for subsequent events: To determine variables having prognostic value regarding recurrent clinical events, information concerning risk factor management, therapy and compliance was obtained from medical records and patient interview. Of the 16 patients with events, 9 (56%) had continued smoking ≥10 cigarettes per day (chi-square = 3.64, $p = 0.06$). There was no statistically significant difference in the frequency of use of antiplatelet agents, warfarin, nitrates, and calcium channel or β blockers in patients with and without repeat events. Non-Q-wave acute MI or reversible thallium defect, the latter finding not unexpected,[13] did not correlate with events after acute MI. Lesion morphology was not useful in predicting future ischemic events, most likely because of the high prevalence of types I and II eccentric lesions in this relatively small group. This lack of predictive power, however, has recently been described in a larger group with more severe residual diameter stenosis after thrombolysis.[14]

DISCUSSION

Recent reports have suggested that the lesion responsible for acute MI has <50% diameter stenosis in 10 to 20% of patients.[2-5] This is consistent with the data regarding the limitations of coronary angiography in correlating lesion severity with potential to produce acute MI.[15] This study expands on these observations by providing baseline and follow-up data on a group of patients with low-grade stenoses demonstrating a tendency to thrombose. This subgroup of patients with acute MI appears to have a high prevalence of young men. Recent studies have characterized such a population in a nonthrombolytic setting.[16,17] Group I is demographically similar to those referenced groups with respect to age, gender and prevalence of tobacco use, and differed significantly in age from the remainder (group II) of this thrombolytic population. The lack of antecedent angina and prior acute MI may also be unique.

Although postdischarge mortality appears low (3%), the follow-up data presented suggest a significant potential for subsequent cardiac events. The role of the original infarct lesion in these clinical events cannot be known with certainty, because ischemia was not documented in all patients with chest pain after acute MI, and silent ischemia was not assessed. The infarct lesion, either by progression to critical stenosis or coronary vasospasm, accounted for 41% of events after acute MI and 58% of documented ischemic episodes. When these lesions are responsible for significant angina or acute MI, they appear to manifest clinically within the first 6 months after acute MI. Reversible coronary vasospasm with ST elevation, as documented in 3 patients during early follow-up, has been reported in the early follow-up of patients who underwent percutaneous transluminal coronary angioplasty, a group that may have a similar pathophysiologic substrate.[18] Recurrent thrombosis at the infarct narrowing is suggested by recurrent total occlusion or relatively rapid "progression" of stenosis over a time course that would be consistent with thrombus formation and inconsistent with atherosclerotic progression. A recent report has suggested a role for thrombus layering at the site of the underlying complex, clinically active lesions,[12] and such a process could have accounted for rapid progression in this group as well as in others noted in published reports.[14,19] In contrast, those clinical events that were probably related to atherosclerotic progression of stenosis at sites of previously nonsignificant disease occurred over a longer duration after acute MI and accounted for 25% of documented clinical ischemia in this group.

A slight degree of underestimation of diameter stenosis can occur for stenoses in this range.[20] However, the lesser likelihood of diffuse disease in patients with no residual or single artery coronary disease should have minimized this. The retrospective design of this study is also a limitation, because type, dosage and route of thrombolysis, duration and intensity of heparinization, and time to angiography may influence the angiographic frequency of these lesions.[2,4,12,17]

Although the data presented here are relatively small and therefore susceptible to statistical error, there was no clear advantage afforded by any particular combination of medical therapies. Smoking may be related to recurrent events, but the data are inconclusive. The relative efficacy of antiplatelet versus anticoagulant therapy versus a combination of therapies (including coronary vasodilators) warrants more detailed investigation.

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Effect of Verapamil on Mortality and Major Events After Acute Myocardial Infarction (The Danish Verapamil Infarction Trial II – DAVIT II)

The Danish Study Group on Verapamil in Myocardial Infarction*

The effect of verapamil on death and major events (i.e., death or reinfarction) after an acute myocardial infarction was studied in a double-blind, randomized, placebo-controlled multicenter trial. Eight hundred seventy-eight patients started treatment with verapamil, 360 mg/day, and 897 patients with placebo. Treatment started in the second week after admission and continued for up to 18 months (mean 16 months). Ninety-five deaths and 146 major events occurred in the verapamil group and 119 deaths and 180 major events in the placebo group. The 18-month mortality rates were 11.1 and 13.8% ($p = 0.11$, hazard ratio, 0.80; 95% confidence limits, 0.61 to 1.05), and major event rates 18.0 and 21.6% ($p = 0.03$, hazard ratio, 0.80; 95% confidence limits, 0.64 to 0.99) in the verapamil and placebo groups, respectively. In patients without heart failure in the coronary care unit the mortality rates were 7.7% in the verapamil group and 11.8% in the placebo group ($p = 0.02$, hazard ratio, 0.64; 95% confidence limits, 0.44 to 0.94), and major event rates 14.6 and 19.7% ($p = 0.01$, hazard ratio 0.70; 95% confidence limits (0.52 to 0.93). In patients with heart failure the mortality rates were 17.9 and 17.5% ($p = 0.79$, hazard ratio, 1.05; 95% confidence limits, 0.72 to 1.54), and major event rates 24.9 and 24.9% ($p = 1.0$, hazard ratio 0.98; 95% confidence limits 0.72 to 1.39).

Long-term treatment with verapamil after an acute myocardial infarction caused a significant reduction in major events, and the positive effect was found in patients without heart failure.

(Am J Cardiol 1990;66:779–785)

Verapamil has been shown in both in vitro and in vivo studies to reduce ischemic injury and infarct size.[1–3] Based on this evidence and a pilot study,[4] the Danish study group on verapamil in myocardial infarction conducted an early intervention, randomized, double-blind, placebo-controlled trial, The Danish Verapamil Infarction Trial (DAVIT I) with the purpose of examining whether administration of verapamil 120 mg 3 times daily preceded by an intravenous bolus of 0.1 mg/kg body weight from the time of admission and the following 6 months might decrease total death and reinfarction rates.[5–7] DAVIT I included 717 patients in the verapamil group and 719 patients in the placebo group. After 6 months' follow-up, nonsignificant differences in mortality rates—12.8% in verapamil versus 13.8% in placebo-treated patients—and in reinfarction rates—7 versus 8.3%, respectively—were found. Retrospective analyses of the data from DAVIT I demonstrated a lower mortality in the verapamil group, 3.7%, compared with 6.4% in the placebo group ($p = 0.05$) between day 22 and 180. The reinfarction rate was 3.9% in the verapamil group compared with 7.0% in the placebo group ($p = 0.03$) between day 15 and day 180.[5–7] The results of DAVIT I were the major reason for the decision to conduct a late intervention study, DAVIT II, the purpose of which was to examine whether treatment with verapamil from the second week after an acute myocardial infarction and continued for 12 to 18 months might reduce total mortality and major events (i.e., death or reinfarction) compared with placebo treatment.

METHODS

Organization: DAVIT II enrolled patients from 20 medical departments with coronary care units with a total catchment population of about 1 million. Each center had a principal investigator. A steering committee of 6 members, representing 5 of the participating centers, was responsible for the operational methods, for monitoring the performance of the clinical centers and for preparing the study report. Two independent observers received interim reports of the results of the trial every 3 months. Furthermore, all information about discontinuation due to adverse drug reactions and about patient deaths was sent to the independent observers for review as soon as possible after the event. Before study initiation it was determined that the independent observers could terminate the trial if there was an unfavorable development of adverse effects in the verapamil group compared with the placebo group.

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*See Appendix.

TABLE I Baseline Characteristics of 1,775 Randomized Patients

	Placebo	Verapamil
	No. (%)	No. (%)
No. of pts.	897 (100)	878 (100)
Sex		
Male	714 (79.6)	702 (80.0)
Female	183 (20.4)	176 (20.0)
Age		
<65 years	577 (64.3)	589 (67.1)
≥65 years	320 (35.7)	289 (32.9)
History		
Previous myocardial infarction	161 (17.9)	138 (15.7)
Hypertension	125 (13.9)	125 (14.2)
Angina pectoris	234 (26.1)	237 (27.0)
Diabetes	50 (5.6)	48 (5.5)
Cigarette smoking	552 (61.5)	557 (63.4)
Complications in coronary care unit		
Shock	35 (3.9)	32 (3.6)
Heart failure	323 (36.0)	291 (33.1)
Cardiac arrest	41 (4.5)	36 (4.0)
Status at randomization		
CT index <50	483 (53.8)	459 (52.3)
CT index ≥50	273 (30.4)	284 (32.3)
CT index not measurable	141 (15.7)	135 (15.4)
Congestion, chest x-ray	58 (6.5)	59 (5.7)
Atrial fibrillation	27 (3.0)	23 (2.6)
Bundle branch block	64 (7.2)	50 (6.7)
Diuretics	375 (41.8)	349 (39.7)
Digoxin	111 (12.4)	98 (11.2)
Antiarrhythmics	21 (2.3)	22 (2.5)
Nitrates other than sublingual	75 (8.4)	69 (7.9)
AMI type and location		
Anterolateral Q-wave	329 (36.7)	318 (36.2)
Inferoposterior Q-wave	315 (35.1)	325 (37.0)
Non-Q-wave	161 (17.9)	141 (16.1)
Other	92 (10.3)	94 (10.7)

AMI = acute myocardial infarction; CT = cardiothoracic.

Design and patient recruitment: The study was a multicenter, double-blind, randomized, placebo-controlled trial of verapamil. All patients below 76 years of age at admission with the diagnosis of acute myocardial infarction were considered eligible. Patients could be enrolled in the study from day 7 to day 15 after admission. All patients without exclusion criteria were included consecutively. Enrollment of patients began in February 1985. According to the study protocol, treatment was to continue for 18 months. However, in case it was necessary to prolong the enrollment period, the last included patient had to be treated for at least 12 months. All treatment of patients ended in January 1989. For administrative reasons 2 centers had to stop follow-up of patients prematurely. This meant that 48 patients were observed for <12 months, 156 patients were observed between 12 and 18 months and 1,571 patients were observed for 18 months (total: 1,775 patients). The average duration of follow-up was 16 months.

Exclusion criteria: Exclusion criteria were heart failure not stabilizing while receiving furosemide ≤160 mg/day; systolic blood pressure below 90 mm Hg; second and third degree atrioventricular block after the third day of admission; sinoatrial block within 3 days of randomization; treatment with β blockers or calcium antagonists due to angina pectoris, arrhythmias or hypertension; the patient's unwillingness to participate, living outside the catchment area or having other severe disabling disease with influence on the prognosis or making outpatient follow-up difficult or impossible; postoperative or posttraumatic infarction; and congenital or significant valvular heart disease.

Study participation could be terminated for the following reasons: patient unwillingness to continue participation, second and third degree atrioventricular block, severe intractable heart failure, angina pectoris or arrhythmias necessitating treatment with β blockers or calcium antagonists and inability to continue treatment because of other severe disease (e.g., cerebral damage). Reinfarction was not a reason for permanent treatment cessation; treatment might be interrupted for up to 2 weeks.

Diagnosis of acute myocardial infarction: We used the same diagnostic criteria as in DAVIT I.[5] Patients were considered for inclusion if they demonstrated chest discomfort, electrocardiographic changes compatible with an acute coronary event and an increase of at least 25% above the upper normal limit in the serum enzymes routinely used in the coronary care units (i.e., creatinine phosphokinase MB, lactate dehydrogenase 1 and aspartate aminotransferase).

Medication: Study medication included verapamil 120 mg 3 times daily or matching placebo. Medication might be reduced to 1 or 2 tablets/day in case of adverse drug reactions. Patients were randomized in blocks of 10 at each center. Study drugs were provided by Knoll Aktiengesellschaft.

Number of patients: When the study was planned in 1984, it was designed to have an 80% power to detect a 30% reduction in total mortality (i.e., $\alpha = 0.05$ and $\beta = 0.2$, 2-sided). With an expected mortality of 13% after 18 months in the placebo group, the trial size estimates suggested that slightly >2,100 patients were needed. This included a 15% allowance for drop outs due to noncompliance or treatment with β blockers or calcium antagonists. Forty percent of all patients with acute myocardial infarction were expected to be included in the study. Inclusion was planned to be completed within 2 years. However, the number of patients with acute myocardial infarction was lower than expected. After 2 years the steering committee decided to extend the inclusion period. The participating departments could only agree to increase the inclusion period for another half year.

End points: The primary end points were total mortality and first major event (i.e., death or reinfarction). To explain a possible effect of verapamil, analyses of sudden death, cardiac death and cardiac events (i.e., cardiac death or reinfarction) were planned, too. A reinfarction had to fulfil the same criteria as the qualifying infarction, or autopsy examination had to demonstrate an acute myocardial infarction. Sudden death meant instantaneous death or death within 1 hour of start of new symptoms, or that the patient was found

TABLE II Reasons for Permanent Treatment Stop

	Placebo No. (%)	Verapamil No. (%)
No. of pts.	897 (100)	878 (100)
Death*	72 (8.0)	48 (5.5)
Second- or third-degree AV block†	7 (0.8)	23 (2.6)
Did not want to continue	61 (6.8)	68 (7.7)
Heart failure	43 (4.8)	50 (5.7)
Angina pectoris	95 (10.6)	74 (8.4)
Antiarrhythmic treatment	14 (1.6)	13 (1.5)
Antihypertensive treatment†	10 (1.1)	0 —
Constipation, abdominal pain†	11 (1.2)	27 (3.1)
Sinus bradycardia, SA block*	2 (0.2)	9 (1.0)
Cannot take oral medication	11 (1.2)	7 (0.8)
Hypotension, dizziness	14 (1.6)	17 (1.9)
Administrative reasons	25 (2.8)	37 (4.2)
Other reasons	16 (1.8)	19 (2.2)
At end of the study period	516 (57.5)	486 (55.4)

* $p < 0.05$; † $p < 0.01$. Overall chi-square = 43.3, $p < 0.01$.
AV = atrioventricular; SA = sinoatrial.

TABLE III Patients Still Receiving Treatment (Status After 12 Months)

	Placebo No. (%)	Verapamil No. (%)
No. of pts.	566 (100)	528 (100)
Trial medication		
3 tablets/day	550 (97.2)	490 (92.8)
Other medication		
Digoxin	58 (10.2)	43 (8.1)
Diuretics*	194 (34.3)	144 (27.3)
Nitroglycerin	164 (29.0)	130 (24.6)
Other nitrates	106 (18.7)	76 (14.4)
Clinical findings		
Angina pectoris	191 (33.7)	151 (28.6)
Dyspnea	83 (14.7)	81 (15.3)
Peripheral edemas	19 (3.4)	24 (4.5)
Pulmonary congestion	8 (1.4)	3 (0.6)
Smoker*	200 (35.3)	221 (41.9)
NYHA group		
I	425 (75.1)	404 (76.5)
II	131 (23.1)	117 (22.2)
III–IV	10 (1.8)	7 (1.3)
Heart rate (beats/min)†	76 ± 11	70 ± 10
Blood pressure		
Systolic (mm Hg)†	141 ± 20	136 ± 18
Diastolic (mm Hg)†	86 ± 11	82 ± 10

* $p < 0.05$; † $p < 0.01$; values are mean ± standard deviation.
NYHA = New York Heart Association.

dead unexpectedly. Cardiac death meant that no other cause of death was diagnosed based on all available information. Autopsy was performed in 43 patients in the verapamil group and in 47 patients in the placebo group. Patient data, autopsy reports and death certificates were sent to the coordinating center. All information about each death was recorded on special data forms independently by 2 members of the steering committee. In case of disagreement about cause and type of death, the data were reviewed by a third member of the steering committee to make a final decision. This evaluation was performed in a blinded manner.

Administration, registration and follow-up: All patients below 76 years of age admitted to the coronary care units with a suspicion of acute myocardial infarction were recorded consecutively on special data forms. All patients with acute myocardial infarction were evaluated for the study. Reasons for exclusion of patients with myocardial infarction were recorded. When a patient was included in the study, the following information was recorded: history before admission, treatment and complications in the hospital, type and location of the infarction, and status at the initiation of study treatment (i.e., heart rate, systemic blood pressure, chest x-ray, electrocardiogram and ongoing therapy). At discharge from the hospital, the clinical status was evaluated again. Repeat evaluations were performed after 1 and 3 months and then every third month up to 18 months. Patients who stopped treatment prematurely would normally be seen after 18 months or at the end of the study period.

Copies of the data forms were sent to the coordinating center and checked before inclusion in the data base.

Information about patient deaths occurring during the study period was obtained on January 31, 1989, from the Central Persons Register, The Ministry of Interior, Copenhagen, where information about deaths in Denmark is registered within 2 weeks.

Ethics: The study was approved by the local ethics committee and the Board of Health. Written and oral information was given to all patients in accordance with the rules of the Central Scientific-Ethical Committee for Denmark. The study was conducted in accordance with the Helsinki declaration.

Data management: The patient data base was constructed using the Scientific Information Retrieval (SIR) Data Base Management System. Each patient was identified by a unique Person Identification Number. At the start of the study the randomization key was loaded into the data base. It was accessible only to the Data Base Administrator, thereby facilitating interim reports for the independent observers.

Using the SIR/FORMS subsystem of SIR, a number of logically connected screen forms were constructed for data entry into the data base. A wide range of logical checks were built into these forms so that data could be extensively checked during entry. Data entry was performed at a terminal situated at the study center in Hillerød immediately when received. No person involved in conduct of the study or member of the steering committee had access to the data base. Data in the SIR data base were processed and moved directly to the BMDP statistical program package for interim and final analyses. Data processing was performed on a CDC CYBER model 825 running the NOS operating system.

Statistical methods: Statistical analyses were performed using the BMDP statistical program package, 1987 version, programs 1D, 3D, 4F, 1L and 2L. Comparison of the 2 treatment groups with respect to baseline and other variables was done with standard tests, such as the chi-square test and the Wilcoxon Mann-Whitney test. Comparison of survival and other event curves was done using the Tarone-Ware test—a life-table method that takes into account variations in follow-up duration and that gives approximately the same weight to early and late events. The comparisons were made on an intention-to-treat basis. Analyses, stratified according to center, were done, too. Statistical tests were 2-sided with an α level of 0.05. Event curves were constructed according to the Kaplan-Meier method.

Hazard ratios and confidence limits for hazard ratios were calculated using the BMDP program for Cox-regression, 2L. Minor discrepancies between the resulting confidence limits and the p values from the Tarone-Ware tests occurred because the hazard ratios are based on the proportional hazards assumption, which is not the case for the Tarone-Ware test.

RESULTS

Description of study groups: In the study period 11,447 patients were admitted to the hospitals a total of 13,771 times; 6,966 patients did not have acute myocardial infarction. Of 4,481 patients with infarction, 490 died before randomization; 2,216 patients were excluded. Major reasons for exclusion were: heart failure (13%), sinoatrial or second or third degree atrioventricular block (11%), treatment with β blockers (18%) or calcium antagonists (19%), other severe disabling diseases (12%), patients not wishing to participate (16%) and patients living outside the catchment area (8%).

One thousand seven hundred seventy-five patients were randomized: 878 patients were randomized to treatment with verapamil and 897 to the placebo group. The 2 groups of patients showed no statistically significant differences in any of the recorded parameters (Table I). Patients were randomized 9 ± 2.7 days (mean ± 1 standard deviation) after admission. For men the mean age was 59.5 ± 9.2 years in the placebo and 58.5 ± 9.4 years in the verapamil group; for women it was 62.4 ± 9.5 years and 62.3 ± 8.7 years, respectively. Women were significantly older than men ($p < 0.01$). At randomization mean heart rate was 75 ± 11 beats/min, systolic blood pressure 120 ± 16 mm Hg and diastolic blood pressure 76 ± 10 mm Hg for both groups. Treatment was stopped permanently before study completion in 392 patients in the verapamil group and in 381 patients in the placebo group (Table II). Based on tablet counts, 86% of the patients in the placebo group and 87% of the patients in the verapamil group had taken at least 90% of the tablets prescribed.

Patients were seen in outpatient clinics 1 and 3 months after discharge and then every third month. Information about status of patients seen in the outpatient clinic after 12 months is presented in Table III. This information is representative of the findings at all status controls. According to the protocol, patients complaining of angina pectoris had to first be treated with isosorbide dinitrate and sublingual nitroglycerin. If a satisfactory result was not obtained with this treatment, trial medication was stopped and treatment with β blockers or calcium antagonists was initiated without breaking the code. Among the patients seen 1 month after discharge, 38.7% (311 of 803 patients) in the placebo group and 33.2% (248 of 748 patients) in the verapamil group ($p = 0.02$) reported attacks of angina pectoris. Over time the proportion of patients still in treatment reporting angina pectoris decreased (Table III); no difference between groups was found after 18 months.

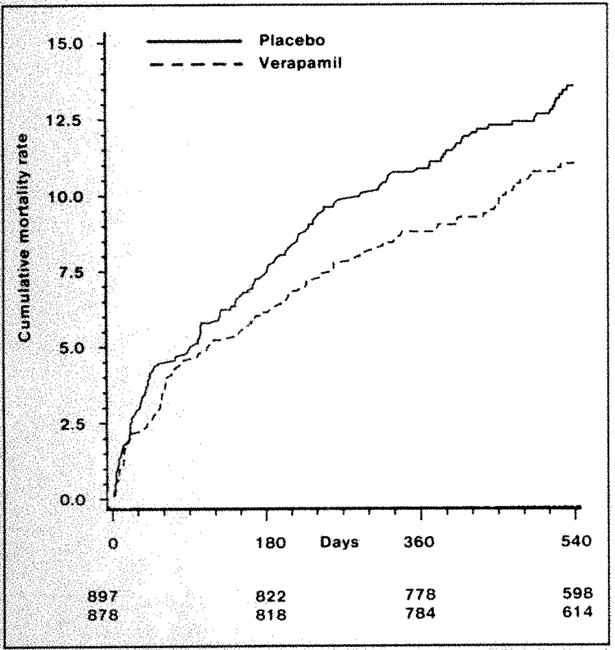

FIGURE 1. Cumulative mortality rate, according to treatment ($p = 0.11$). The number of patients at risk are shown at the *bottom* (placebo, n = 897; verapamil, n = 878).

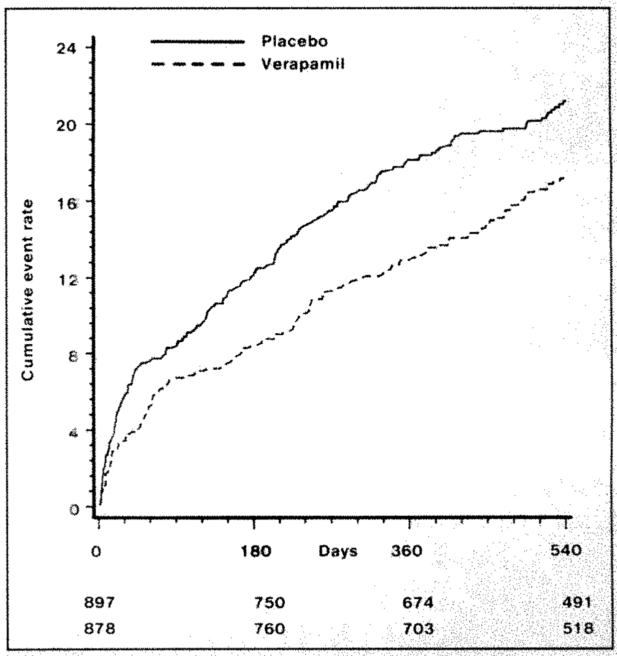

FIGURE 2. Cumulative major event rate, according to treatment ($p = 0.03$). The numbers of patients at risk are shown at the *bottom* (placebo, n = 897; verapamil, n = 878).

TABLE IV Number of End-Point Events, 18-Month Event Rates and Hazard Ratio According to Treatment Group

	Placebo		Verapamil				
Event	No. of Pts.	Event Rate (%)	No. of Pts.	Event Rate (%)	p Value	Hazard Ratio	95% Confidence Limits
All patients	897	(–)	878	(—)	—	—	—
Total death	119	(13.8)	95	(11.1)	0.11	0.80	0.61, 1.05
First major event	180	(21.6)	146	(18.0)	0.03	0.80	0.64, 0.99
Cardiac death	107	(12.3)	84	(9.9)	0.10	0.79	0.59, 1.05
Sudden death	63	(7.4)	46	(5.6)	0.10	0.74	0.50, 1.07
First reinfarction	107	(13.2)	84	(11.0)	0.04	0.77	0.58, 1.03
First cardiac event	170	(20.2)	137	(17.0)	0.03	0.80	0.64, 1.00
No heart failure	574	—	587	—			
Total death	64	(11.8)	43	(7.7)	0.02	0.64	0.44, 0.94
First major event	104	(19.7)	78	(14.6)	0.01	0.70	0.52, 0.93
First reinfarction	66	(12.7)	48	(9.4)	0.02	0.67	0.46, 0.97
First cardiac event	97	(18.0)	74	(13.9)	0.01	0.71	0.52, 0.96
Heart failure	323	—	291	—			
Total death	55	(17.5)	52	(17.9)	0.79	1.05	0.72, 1.54
First major event	76	(24.9)	68	(24.9)	0.98	1.00	0.72, 1.39
First reinfarction	41	(14.2)	36	(14.3)	0.89	0.98	0.63, 1.54
First cardiac event	73	(24.0)	63	(23.1)	0.81	0.97	0.69, 1.35

First major event = first reinfarction or death; First cardiac event = first reinfarction or cardiac death.

This is in accordance with the finding that angina pectoris was more often the major reason for permanent treatment cessation in the placebo group than in the verapamil group (Table II).

End points: Intention-to-treat analyses (Table IV) demonstrated after 18 months a statistically nonsignificant reduction in total mortality in the verapamil group compared with the placebo group (Figure 1) and statistically significant reduction of first major events in the verapamil group (Figure 2). The total number of reinfarctions (including second and third reinfarctions) was 91 in the verapamil group and 129 in the placebo group—a reduction of 29% for all recorded reinfarctions. The 18-month first reinfarction rate was significantly reduced in the verapamil group.

Before breaking the code, we elected to perform a number of subgroup analyses. The variables were gender, age above and below 65 years, previous myocardial infarction, cardiac arrest in the coronary care unit, atrial fibrillation, angina pectoris, type and location of the myocardial infarction, and heart failure at any time before randomization during stay in the coronary care unit. Interaction analyses demonstrated that only information about heart failure was related to event rates (Table IV, Figure 3).

DISCUSSION

Animal experiments have demonstrated that treatment with verapamil before an ischemic injury reduces infarct size.[1–3,8] Continuation of the treatment after coronary artery occlusion maintains the beneficial effect of verapamil.[9] Pretreatment prevents postischemic stunning as well.[10] Extrapolating from these animal experiments to humans, the best opportunity to prevent or limit infarct size should occur with prophylactic treatment with verapamil.[1,8] The experimental findings are in accordance with the retrospective analyses of the results of DAVIT I.[5–7] Verapamil is effective in prevention of ischemic episodes in patients with stable angina pectoris,[11] unstable angina,[12,13] vasospastic angina[14] and silent ischemia.[13,15] Verapamil reduces the prevalence of ventricular ectopic beats[7] and may prevent exercise-induced ventricular tachycardia.[16,17] These findings support the hypothesis that verapamil may reduce myocardial ischemia and prevent arrhythmias after a myocardial infarction.

DAVIT II was conducted to ascertain if treatment with verapamil reduced total death and major events. As we anticipated when planning the study, 40% of the patients with acute myocardial infarction had no exclusion criteria and were randomized. Mortality rates in the placebo group after 12 and 18 months were 10.8 and 13.8%—well in accordance with the expected values of 10 and 13%, respectively. There were 1,775 patients; we initially planned to include 2,100. The enrollment was lower because 2 departments stopped inclusion of patients for administrative reasons and 1 department was closed. Because of the lower number of patients, the statistical power of the study is slightly reduced compared with the study plan. There was a 100% confirmation of mortality. Nonfatal reinfarctions were likewise recorded with great certainty, because patients were normally readmitted to the same department and only 110 patients in the placebo and 111 patients in the verapamil group were not seen in the outpatient clinic at the end of the study period.

The important result of this study is a significant reduction in major and cardiac events. The effect of verapamil might be related to a reduction in myocardial ischemia, as demonstrated by the lower prevalence of angina pectoris in the verapamil group compared with the placebo group. The effect of verapamil might also be related to the significantly lower heart rate and blood pressure occurring during verapamil treatment compared with placebo treatment (Table III).

The subgroup analyses presented were planned before termination of patient follow-up in DAVIT II. The analyses (Table IV) demonstrated that patients without heart failure in the coronary care unit had a significantly better prognosis than patients with heart failure. Verapamil caused a significant reduction of 18-month mortality, major event, cardiac event and reinfarction rates in patients without heart failure. No significant differences were found between the 2 treatment groups in patients with heart failure. The overall positive effect of verapamil was thus found in patients without a history of heart failure in the coronary care unit immediately before randomization. The effect of verapamil in patients without heart failure corresponds to the findings of the Multicenter Diltiazem Postinfarction Trial (MDPIT)[18] that diltiazem reduced cardiac events in patients without heart failure. But, contrary to diltiazem, verapamil had no harmful effect in patients with heart failure.

Other studies: Two other large-scale late intervention postinfarction double-blind, placebo-controlled trials have been conducted with calcium antagonists: The Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT)[19] and MDPIT.[18] The protocols of these 2 trials are similar to the DAVIT II protocol, although we excluded patients in need of β-blocker therapy due to angina pectoris, arrhythmias or hypertension, and we did not use β blockers as secondary prophylaxis after an acute myocardial infarction. Twenty percent of the patients in SPRINT and about 55% of the patients in MDPIT were receiving β-blocker treatment at the time of randomization. The inclusion rate was 40% in DAVIT II compared with 48% in SPRINT and 18% in MDPIT. The 1-year mortality rate in the placebo groups of SPRINT and MDPIT was approximately 6 to 7%; the rate was 10.8% in the DAVIT II placebo group. It is also of interest to note that 32% of the 251 deaths in the diltiazem study were classified as noncardiac compared to 18% of 132 in SPRINT and 15% of 214 deaths in DAVIT II. The SPRINT, where 30 mg nifedipine/day was given, found 10-month mortality and nonfatal reinfarction rates of 5.7 and 4.8% in the placebo group and 5.8 and 4.4% in the nifedipine group (difference not significant). The patients in MDPIT received 240 mg diltiazem/day. After a mean observation period of 25 months, the mortality rates in the placebo and diltiazem groups were equal at about 16%, and the cardiac event rates (i.e., cardiac death and nonfatal reinfarction) were about 20 and 18%, respectively. Thus, neither nifedipine nor diltiazem were demonstrated to have any overall beneficial effect on mortality or reinfarction rates after an acute myocardial infarction. The lack of effect of nifedipine might be explained by the pronounced vasodilator properties of nifedipine often associated with increase in heart rate. The lack of effect of diltiazem might be related to the simultaneous β-blocker treatment in about 55% of the patients. If the 2 types of drugs are influencing the same factors, no further effect could be expected by adding diltiazem to β blockers.[20]

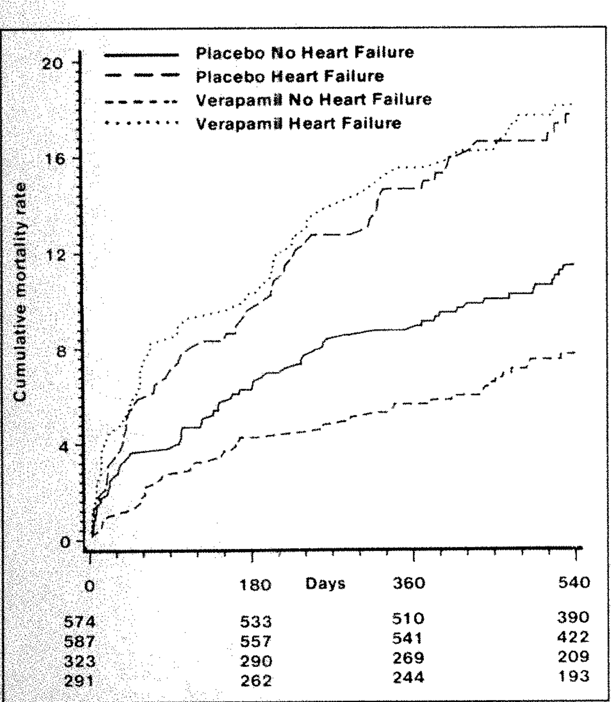

FIGURE 3. Cumulative mortality rates in patients with (difference not significant) and without heart failure (p = 0.02), according to treatment. The numbers of patients at risk are shown at the *bottom* (placebo, no heart failure, n = 574; verapamil, no heart failure, n = 587; placebo, heart failure, n = 323; verapamil, heart failure, n = 291).

Held et al[21] recently gave an overview of calcium antagonists in acute myocardial infarction and unstable angina. Analyses of 2 acute and long-term trials[5,22] and 3 long-term trials[18,19,23] demonstrated a slightly increased mortality in the calcium antagonist-treated patients compared with the placebo-treated patients. Their conclusion was that calcium antagonists cannot be recommended for routine use after an acute myocardial infarction. It is questionable whether it is reasonable to combine data from trials performed with drugs with such highly differing pharmacologic profiles as lidoflazine,[23]nifedipine,[19,22] diltiazem[18] and verapamil.[5]

Yusuf et al[24] recently presented an extensive review of early and late intervention trials in patients after an acute myocardial infarction based on meta-analyses. For patients treated with β blockers compared with placebo-treated patients they calculated a reduction in pooled odds ratio of mortality of 22% (95% confidence interval, 16 to 30%) and of reinfarction of 27% (confidence interval, 17 to 37%). The findings of DAVIT II, with a reduction in hazard ratios of 20 to 26% for verapamil-treated patients compared with placebo-treated patients (Table IV), correspond to the effect of β blockers. From a clinical viewpoint verapamil may be considered an alternative to β blockers as secondary prophylaxis after an acute myocardial infarction.

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APPENDIX

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Impact of Field-Transmitted Electrocardiography On Time to In-Hospital Thrombolytic Therapy in Acute Myocardial Infarction

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To assess the impact of a field-transmitted electrocardiogram (ECG) on patients with possible acute myocardial infarction, randomized and open trials were performed with a portable electrocardiographic system coupled with a cellular phone programmed to automatically transmit ECGs to the base hospital. Consecutive patients served by the 6 units of the Salt Lake City Emergency Rescue System were studied; 71 patients were randomized to in-field ECG (n = 34) versus no ECG (n = 37). Time on scene was 16.4 ± 9.7 minutes for the ECG group versus 16.1 ± 7.0 minutes for the non ECG group (difference not significant). Time of transport averaged 18.2 ± 9.9 and 17.6 ± 13.1 minutes, respectively (difference not significant). Six of 34 patients with in-field ECG showed acute myocardial infarction, qualified for and received thrombolytic therapy at 48 ± 12 minutes after hospital arrival (range 30 to 60) compared with 103 ± 44 minutes ($p < 0.01$) for 51 historical control patients and 68 ± 29 minutes for 6 concurrent control patients without in-field ECG. Thus, in-field ECG causes negligible delays in paramedic time, leads to significant decreases in time to in-hospital thrombolysis and may make in-field therapy feasible. In-field ECG may be an important addition to reperfusion strategies.

(Am J Cardiol 1990;66:786–791)

In the past decade, thrombolytic reperfusion has become established therapy in acute myocardial infarction (AMI),[1,2] now known to be precipitated by coronary thrombosis[3,4] and to evolve rapidly after coronary occlusion.[5] Early application of therapy has been shown to be important to achieve early reperfusion[6,7] to improve left ventricular function and decrease infarct size[8-14] and to decrease mortality.[15-17] Treatment given in <2 to 4 hours after symptom onset has consistently yielded greater benefit than later treatment[9-11,15,17] and even earlier therapy (within 1 to 2 hours) is desirable.[11,15,17]

Delays in administering thrombolytic therapy include not only patient delays and transport time, but also hospital delays after arrival.[18-20] Paramedic transmission of an in-field, 12-lead electrocardiogram (ECG) to physicians at the base hospital is a newly available approach to decreasing delay to AMI diagnosis[21] and treatment.[22,23] However, additional experience from controlled studies would be useful to establish the reliability and impact of in-field ECG before embarking on its extensive use, including the guidance of in-field thrombolytic therapy.[22-24] This study assesses the feasibility and impact of field-transmitted ECG on the prehospital and early hospital care of patients with suspected AMI in a randomized design.

METHODS

The purpose of phase I of the Field Ambulance Study of Thrombolysis in Myocardial Infarction (FAST-MI) was to show the feasibility and advisability of using an in-field ECG to direct the initiation of thrombolytic therapy in a randomized, dry-run study design before initiating Phase II (currently underway) of the treatment study (initiating therapy in-field versus in-hospital).

Study objectives and hypotheses: Specific study objectives were the following: to assess the feasibility of obtaining and transmitting the in-field electrocardiogram (ECG) to the base hospital; to evaluate and compare the natural history of in-field evaluation and transport of chest pain patients both with and without knowledge of the field-transmitted ECG; and to determine the reliability and "safety" of paramedic/emergency physician diagnosis of AMI and triage to thrombolytic therapy. We hypothesized that the in-field ECG could be obtained successfully and without substantial delay and that appropriate patient triage could be made. The study was approved by the LDS Hospital Institutional

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From the Department of Medicine, Division of Cardiology and LDS Hospital, Salt Lake City, Utah. This study was supported in part by a grant from Genentech Inc., South San Francisco, California. Manuscript received January 31, 1990; revised manuscript received and accepted May 11, 1990.

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Review Board and by the Utah State Department of Health, Emergency Services Division.

Study design: The study was designed in 2 parts—an education phase and a study phase.

Education phase: The Salt Lake City Paramedic Rescue Units serve a population base estimated at 600,000 people. Initially, 2 training sessions were conducted in a prefield setting for the 6 paramedic units (50 personnel). Subsequently, in-field training was provided at least twice for each paramedic unit. Concurrently, training of emergency room physicians and nurses was undertaken in receiving and reviewing field-transmitted ECGs and in randomizing patients to "mock" in-field initiated versus emergency room initiated therapy. A start-up phase was then undertaken, consisting of a series of consecutive ECGs in chest pain patients (≥ 10 per paramedic unit) to show the ability to correctly use the equipment.

Study phase: After study initiation, consecutively evaluated patients were selected for an ECG based on the clinical (paramedic's) suspicion of possible AMI (i.e., suggestive chest pain) alone. (Further clinical evaluation—e.g., assessment of other inclusion/exclusion criteria for "mock" thrombolytic therapy—was considered afterward in patients with a diagnostic ECG.) Paramedics randomized "ECG-eligible" patients at the scene to obtain or not to obtain an in-field ECG by opening a sealed envelope. Records were kept of the actual time spent in attending to the patient at the scene, the time in transport and the time to thrombolytic therapy if given after hospital arrival. Phase I was prospectively planned to run for 3 months or until >50 patients over the age of 35 years were evaluated. A flow chart of the study is shown in Figure 1.

In-field electrocardiographic assessment: An in-field 12-lead ECG was performed by means of a battery-powered portable electrocardiograph weighing 28 lbs (Marquette, Inc.). The ECG was usually performed on-scene, but occasionally in-transport. Both an on-scene 12-lead ECG printout and a hospital printout, both with ECG interpretation (Marquette Diagnosis Program Software), were provided by the system with minimal delay (<1 min).

Patients were considered for "mock" thrombolytic therapy if they gave a history of chest pain suggestive of ischemia of ≥ 20 minutes duration despite nitroglycerin, had electrocardiographic evidence of transmural injury (≥ 0.1 mV ST elevation in ≥ 2 limb leads and/or ≥ 0.2 mV in ≥ 2 precordial leads), were <76 years old and had no contraindications (Figure 2). For these patients, the emergency room physician reviewed by telephone the exclusion list (Figure 2) with the paramedics. In qualifying patients, randomization was made to "mock" in-field versus in-hospital thrombolytic therapy by means of a consecutively numbered envelope.

Analysis: Time at scene and time in transport were averaged for the 2 assignment groups and compared by Student's t test. Time delays were also assessed from emergency room arrival to thrombolytic therapy and were compared among patients receiving treatment in this Phase I study, patients concurrently treated but not entered into FAST-MI and a historically treated group. A comparison between initial (emergency physician/paramedic) and retrospective (cardiologist) assessment of AMI was also made. Averaged data are generally presented as mean ± standard deviation. A p value <0.05 was considered statistically significant.

RESULTS

Randomized phase: The randomized portion of Phase I was conducted over a period of 3 months (December 1988 to March 1989). A total of 180 calls were received for chest pain; 71 (39%) of these patients were

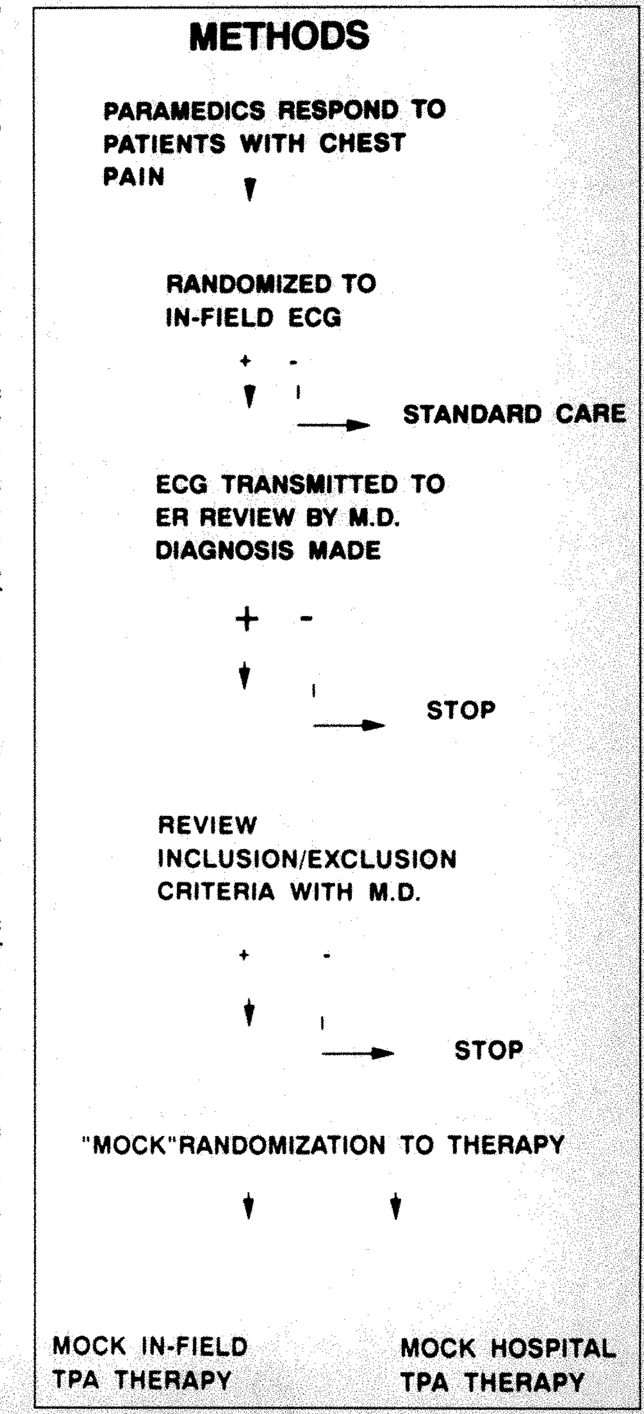

METHODS
PARAMEDICS RESPOND TO PATIENTS WITH CHEST PAIN
RANDOMIZED TO IN-FIELD ECG
+
-
STANDARD CARE
ECG TRANSMITTED TO ER REVIEW BY M.D. DIAGNOSIS MADE
+
-
STOP
REVIEW INCLUSION/EXCLUSION CRITERIA WITH M.D.
+
-
STOP
"MOCK"RANDOMIZATION TO THERAPY
MOCK IN-FIELD TPA THERAPY
MOCK HOSPITAL TPA THERAPY

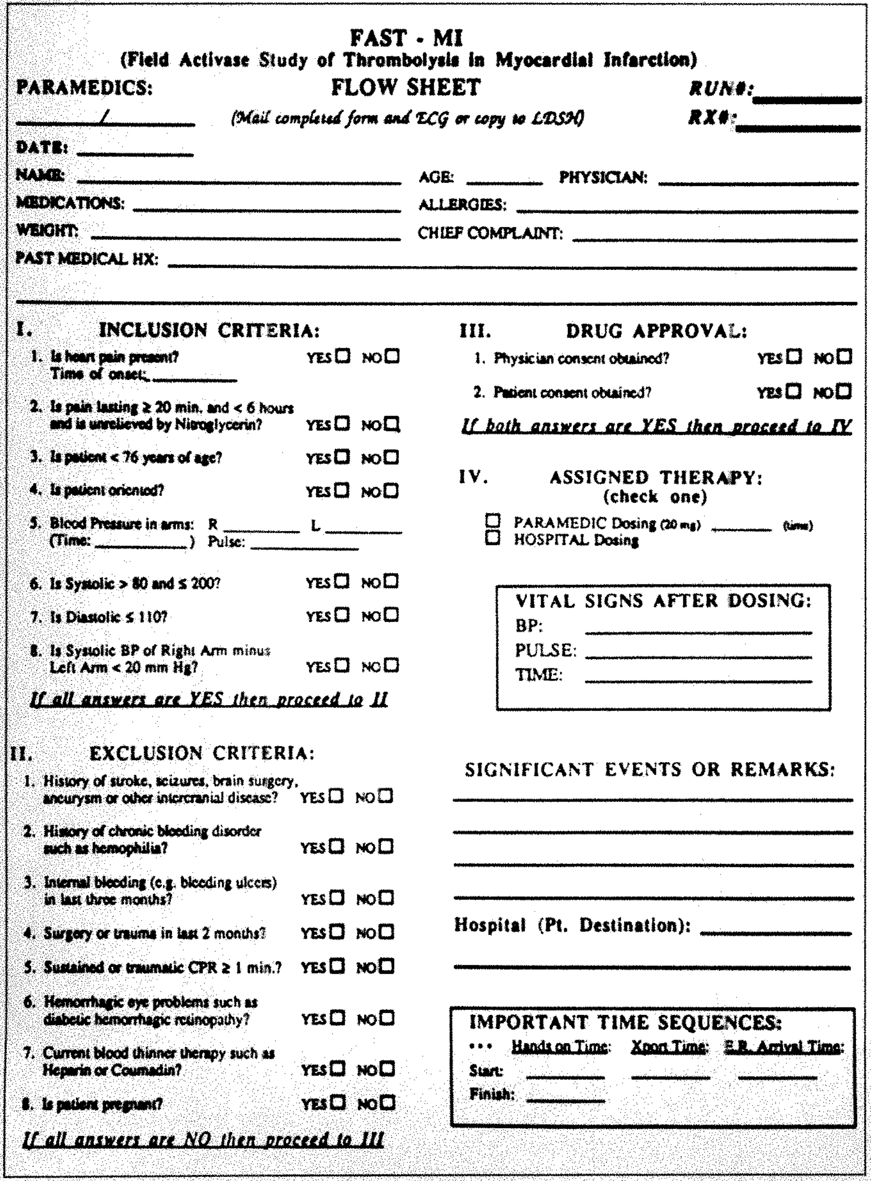
FIGURE 1. Flow chart showing general study design and decision tree. ECG = electrocardiogram; ER = emergency room.

judged by paramedics to represent possible ischemia and were randomized; 34 were randomized to receive in-field ECG and 37 to no ECG.

Impact of in-field electrocardiogram on prehospital time: Assignment to the in-field ECG group caused a negligible overall impact on time spent at the scene (Figure 3) and on time in transport (Figure 4). Time spent on the scene averaged 16.4 ± 9.7 minutes for the in-field ECG group ($n = 34$) and 16.1 ± 7.0 minutes for the nonECG group ($n = 37$, difference not significant). The range of times at the scene was 2 to 36 minutes for the ECG group and 4 to 50 minutes for the nonECG group. Transport time from the scene to the hospital averaged 18.2 ± 1.7 minutes in the ECG group and 17.6 ± 2.2 minutes in the nonECG group. The range of transport times was 4 to 40 minutes for the ECG group and 3 to 50 minutes for the nonECG group.

Diagnosis and confirmation of acute myocardial infarction based on in-field electrocardiogram: A total of 6 (17%) of the 34 patients receiving in-field ECG were diagnosed by the emergency physician/paramedic team as having an AMI. On retrospective (cardiologist) electrocardiographic review, the diagnosis was confirmed in 5 and was equivocal in 1. The ECGs were confirmed to show no MI in the other 28. Two other patients were diagnosed as having AMI by in-field ECG among 16 additional patients with possible AMI studied in the start-up phase, before beginning the randomization protocol. Of these 8 patients with AMI, 3 were ineligible, 2 because of age ≥76 years and 1 because of cardiac arrest requiring resuscitation measures.

Time to thrombolytic therapy after in-field electrocardiogram: Of patients receiving in-field ECG, 5 showing AMI qualified for and received thrombolytic therapy in-hospital. In these patients, the time from hospital arrival to initiation of therapy averaged 48 ± 12 minutes (range, 30 to 60 minutes). This compares favorably with 103 ± 44 minutes ($p < 0.01$) for 51 historical control patients entered into thrombolytic therapy studies over the previous 3 years (Figure 5), and 68 ±



FAST - MI
(Field Activase Study of Thrombolysis in Myocardial Infarction)
PARAMEDICS: **FLOW SHEET** ***RUN#:*** ______
______/______ *(Mail completed form and ECG or copy to LDSH)* ***RX#:*** ______

DATE: ______
NAME: ______ **AGE:** ______ **PHYSICIAN:** ______
MEDICATIONS: ______ **ALLERGIES:** ______
WEIGHT: ______ **CHIEF COMPLAINT:** ______
PAST MEDICAL HX: ______

I. INCLUSION CRITERIA:

1. Is heart pain present? YES ☐ NO ☐
   Time of onset: ______
2. Is pain lasting ≥ 20 min. and < 6 hours and is unrelieved by Nitroglycerin? YES ☐ NO ☐
3. Is patient < 76 years of age? YES ☐ NO ☐
4. Is patient oriented? YES ☐ NO ☐
5. Blood Pressure in arms: R ______ L ______
   (Time: ______) Pulse: ______
6. Is Systolic > 80 and ≤ 200? YES ☐ NO ☐
7. Is Diastolic ≤ 110? YES ☐ NO ☐
8. Is Systolic BP of Right Arm minus Left Arm < 20 mm Hg? YES ☐ NO ☐

If all answers are YES then proceed to II

II. EXCLUSION CRITERIA:

1. History of stroke, seizures, brain surgery, aneurysm or other intercranial disease? YES ☐ NO ☐
2. History of chronic bleeding disorder such as hemophilia? YES ☐ NO ☐
3. Internal bleeding (e.g. bleeding ulcers) in last three months? YES ☐ NO ☐
4. Surgery or trauma in last 2 months? YES ☐ NO ☐
5. Sustained or traumatic CPR ≥ 1 min.? YES ☐ NO ☐
6. Hemorrhagic eye problems such as diabetic hemorrhagic retinopathy? YES ☐ NO ☐
7. Current blood thinner therapy such as Heparin or Coumadin? YES ☐ NO ☐
8. Is patient pregnant? YES ☐ NO ☐

If all answers are NO then proceed to III

III. DRUG APPROVAL:

1. Physician consent obtained? YES ☐ NO ☐
2. Patient consent obtained? YES ☐ NO ☐

If both answers are YES then proceed to IV

IV. ASSIGNED THERAPY:
(check one)

☐ PARAMEDIC Dosing (20 mg) ______ (time)
☐ HOSPITAL Dosing

VITAL SIGNS AFTER DOSING:
BP: ______
PULSE: ______
TIME: ______

SIGNIFICANT EVENTS OR REMARKS:

Hospital (Pt. Destination): ______

IMPORTANT TIME SEQUENCES:

•••	Hands on Time:	Xpon Time:	E.R. Arrival Time:
Start:	______	______	______
Finish:	______		

FIGURE 2. Paramedic information and questionnaire form for in-field patient screening and enrollment. FAST-MI = Field Ambulance Study of Thrombolysis in Myocardial Infaction.

29 minutes for 6 concurrently treated patients receiving thrombolytic therapy during the 3-month period of the Phase I study but not having in-field ECG.

DISCUSSION

Study summary: Phase I of our FAST-MI study showed the feasibility, efficiency and reliability of in-field ECG acquisition by a paramedic/emergency physician team in evaluating chest pain calls for a representative urban/suburban population. The equipment was easily adapted to paramedic use. During the education and start-up phases, a number of minor technical difficulties were addressed and overcome. In the randomized phase, increases beyond the previous average of 35 minutes total time at the scene and in transport were minimal (nonsignificant). Agreement between emergency physician (prospective) and cardiologist (retrospective) diagnosis of AMI was good; no false negative diagnoses and only 1 equivocal false positive diagnosis occurred. However, these numbers are small and further observations are needed. Importantly, the time from hospital arrival to initiation of thrombolytic therapy was decreased by about 40 minutes compared with that in our recent study experience.[7] A decrease of 20 minutes to therapy was also achieved when compared with a concurrent group of treated patients not receiving in-field ECG.

Reasons for delay in initiating thrombolytic therapy: Delays to thrombolytic therapy after hosptial arrival appear to contribute more to overall delay to thrombolytic therapy than either transport time or patient delay in seeking medical assistance.[19] In a recent Minnesota study,[20] in-hospital delays accounted for more than half of the total time from onset of symptoms to initiation of thrombolysis. Of the total hospital delay of 90 minutes, 20 minutes were due to the initial ECG. Other delays were less when drugs were administered in the emergency department (47 minutes) than after transfer to the coronary care unit (82 minutes). Similar hospital delays were observed in both our recent historical experience (108 minutes)[7] and in an earlier Western Washington trial (102 minutes).[22]

In-hospital delays in initiating therapy include the following: administrative reasons (registration, triage, overcrowding/bed problems); diagnostic evaluation (nurse, physician evaluation; ECG, blood, x-ray tests); therapeutic needs (starting intravenous lines); medical/political reasons (consultations among private physician, cardiologist, house staff); and pharmacy delays (obtaining, mixing, administering drug).[19]

Impact of in-field electrocardiogram on hospital delays: Transmission of an in-field ECG alerts the hospital-based medical care team in advance that an incoming patient has an AMI. These hospital delays may

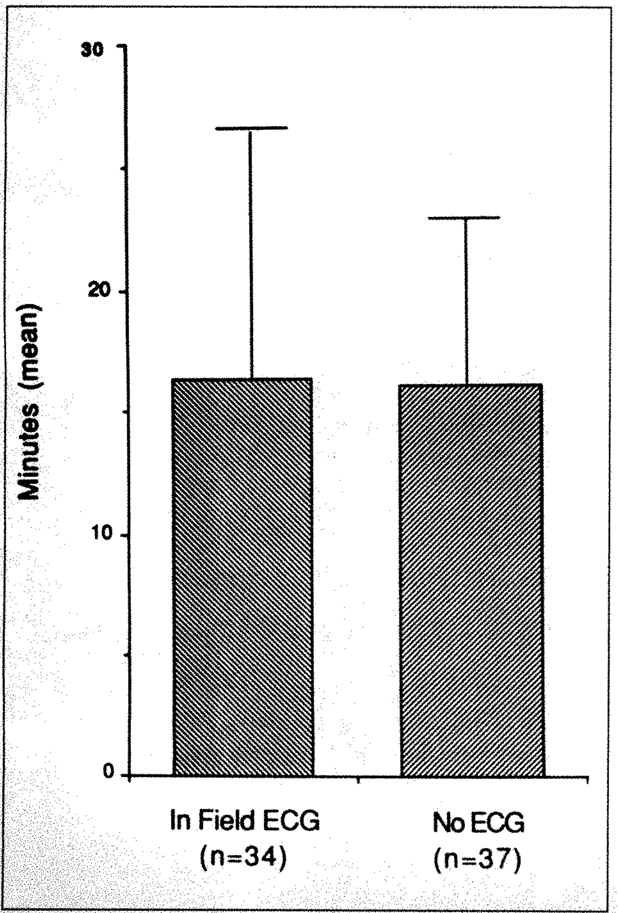


FIGURE 3. Paramedic time (mean ± standard deviation [min]) spent on-scene for patient pickup in groups randomized to receive an in-field ECG and no ECG.

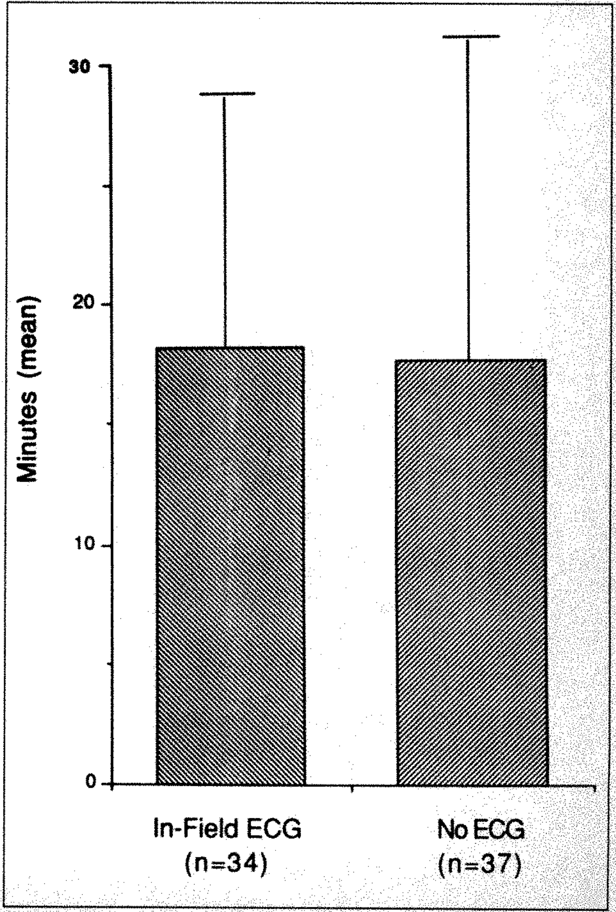


FIGURE 4. Transport time (mean ± standard deviation [min]) from scene of patient pickup to hospital in groups randomized to receive an in-field electrocardiogram (ECG) and no ECG.

then be shortened because the process of preparing for thrombolytic therapy may begin well in advance of patient arrival (about 30 minutes in our study). The time saved to the first ECG appears to be directly passed on in time saved to thrombolytic therapy. In the Seattle experience, in-hospital delay was decreased from 102 to 46 minutes after instituting an in-field ECG system[22] (Figure 5). Similarly, we saw a decrease from 108 to 48 minutes (Figure 5). Part of this decrease may also reflect better training of emergency room personnel in screening patients and greater involvement in initiating therapy, as suggested by the decrease in delay noted recently in our studies (108 to 68 minutes) and in others',[20,22] even in patients not receiving in-field ECG.

Demography of chest pain patients evaluated by paramedics: Only a small minority of patients with chest pain attended to by paramedics have electrocardiographic and clinical characteristics of AMI that qualify them for thrombolytic therapy, an observation of importance to the planning of future intervention studies. In our study, 39% (71 of 180) of total chest pain calls were judged clinically to represent possible AMI and of these, only 17% receiving in-field ECG showed AMI. Thus, only about 7% of chest pain calls were identified in-field as an AMI. Of the 8 patients showing AMI by in-field ECG, 5 qualified for thrombolytic therapy (63% of AMI patients but only 3 to 4% of all chest pain calls). Similarly, in the larger Seattle experience, 3% (83/2,465) of patients calling with chest pain met criteria for possible prehospital thrombolytic therapy.[22] Patients were excluded most commonly because of a nondiagnostic ECG, pain >6 hours, age ≥75 years and hypertension.[22] Further, of patients who gradually developed an AMI in-hospital, only 20% met prehospital criteria for therapy and 22% more qualified for therapy after initial hospital evaluation.

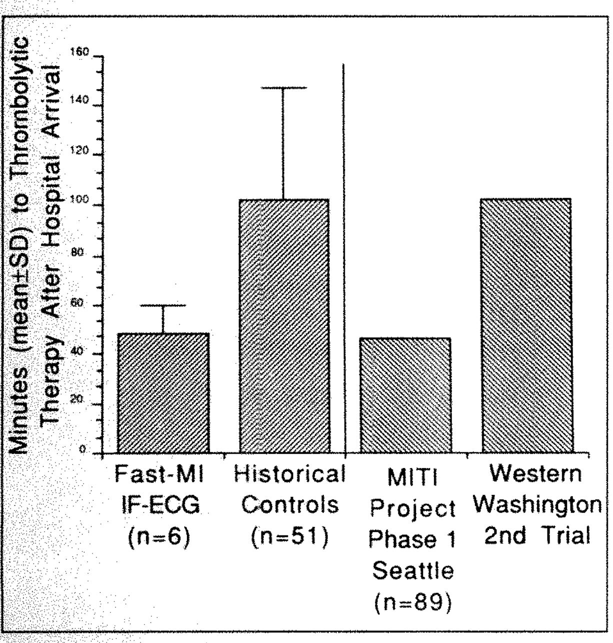


FIGURE 5. Times to thrombolytic therapy after hospital arrival. *Left,* patients with acute myocardial infarction who received an in-field electrocardiogram (IF-ECG) compared with recent historical control patients *(right)* not getting IF-ECG; *Right,* a literature comparison also showing treatment times for patients receiving IF-ECG *(left hand bar)* and historical control subjects without IF-ECG *(right hand bar).*

Similarly, in a New England study, only 23% (261 of 1,118) of patients who eventually developed an AMI were candidates for thrombolysis in the emergency room based on age ≤75 years, pain for <4 hours and a diagnostic ECG,[23] before accounting for exclusions due to contraindications to thrombolysis. Of some concern was their estimate that for every patient treated with true positive findings (based on the interpretation of a single ECG), 1 to 2 patients with false positive results might be treated. Fortunately, this last conjecture has not been substantiated in clinical trials in which, generally, ≥95% of patients have subsequently showed an AMI.[7,15,16]

Implications for in-field thrombolysis: Our study supports the feasibility of initiating thrombolytic therapy in-field but also emphasizes the need for controlled trials before embracing in-field therapy. Our experience in the FAST-MI is consistent with that of others that suggest that a good, although not perfect, correlation exists between emergency physician/computer diagnosis of AMI and cardiologist (retrospective) diagnosis. Using similar technology, the University of Washington group achieved a 70% sensitivity and a 100% specificity for a computer-based diagnosis algorithm (Marquette System Diagnosis Program) of AMI.[24] Although this exceptional specificity will require further confirmation, the results do suggest that a computer based system may help prevent over-diagnosis of AMI[19,23] and potentially hazardous[25] overuse of thrombolytic therapy by emergency room personnel less experienced in ECG interpretation.

Improved accuracy in diagnosis and therapy might also be achieved by having well-trained physicians travel with paramedic units.[11,26] However, this approach does not appear to be practical in the United States.

Another approach to optimizing both safety and efficacy may be to use a small "priming" dose of a short-acting thrombolytic agent in the field to begin the process of thrombolysis. Review of the decision to give full-dose therapy could then be made in the emergency room and therapy effectively terminated if desired. Tissue plasminogen activator (alteplase) has the properties of excellent hemodynamic tolerance, rapidly acting thrombolytic effect and a short half-life. The efficacy and safety of "front-loaded" (bolus initiated) regimens of alteplase have been recently evaluated and appear to be promising.[27] Based on these characteristics of alteplase, we believe that the administration of an in-field loading bolus (i.e., 20 mg) by paramedics, followed by continuation of a full-dose regimen upon hospital arrival, represents an appealing regimen to test (FAST-MI, Phase II). However, given the potentially dire consequences of misapplication of thrombolytic therapy[25] and both medical and legal concerns about paramedic administration of thrombolytic therapy, we believe that streamlined in-hospital (emergency department) initiation of therapy should be currently viewed as the best strategy for initiating thrombolytic therapy.[19] Whether or not in-field initiation of therapy is safe and will give additional benefit must be addressed in ongoing or future studies.[22,28]

Acknowledgment/Appendix: We recognize the participation and performance of the following rescue units of the Salt Lake City Paramedic System: numbers 2, 3, 5, 7, 8 and 11. Hospitals receiving patients from the Salt Lake Paramedic System include the following: LDS Hospital; Holy Cross Hospital; University of Utah Hospital; Veterans Administration Hospital; St. Marks' Hospital; Cottonwood Hospital; and Lakeview Hospital. Principal investigators of the FAST-MI study were the following: Study principal investigator, Jeffrey L. Anderson; Co-investigator, Labros Karagounis; Study Coordinator, Steven Ipsen, RN; Co-coordinator, Ann Allen; and Graphics, John Carlquist, PhD. Specific hospital investigators were the following: LDS Hospital, L. Karagounis, J. Anderson; Holy Cross Hospital, S. Nichols, T. Keith; University Hospital, R. Freedman; Veterans Administration Hospital, R. Sutton; and St. Mark's and Cottonwood Hospitals, J. Perry. We acknowledge the associated members of the Paramedic System and LDS Hospital Emergency Department, as well as the attending physicians and nurses. We recognize Sam Teichman, MD, Study Sponsor, Genentech, South San Francisco, California; and Mark Zyvoloski and Michael Fletcher, Marquette Inc., Milwaukee, Wisconsin.

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Sensitivity of a Set of Myocardial Infarction Screening Criteria in Patients with Anatomically Documented Single and Multiple Infarcts

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A subset of 3 screening criteria (Q wave ≥30 ms in lead aVF, any Q or R wave ≤10 ms and ≤0.1 mV in lead V_2, and R wave ≥40 ms in V_1) has been proposed to identify single nonacute myocardial infarcts. Cumulatively, these 3 criteria achieved 95% specificity, and 84 and 77% sensitivities for inferior and anterior myocardial infarcts, respectively, among patients identified by coronary angiography and left ventriculography. This study establishes the true sensitivities of the set of screening criteria in 71 patients with anatomically proven single myocardial infarcts and 32 patients with multiple myocardial infarcts. In the single inferior infarct group, the aVF criterion was 90% sensitive. The V_2 criterion (any Q or R wave ≤10 ms and ≤0.1 mV) was 67% sensitive in the single anterior infarct group. No single criterion proved sensitive in identifying a posterolateral infarct. The set of screening criteria performed just as well for multiple infarcts as it did for single infarcts, with a cumulative sensitivity of 72%. The overall sensitivity of the screening set in the 103 patients in all groups was 71%.

(Am J Cardiol 1990;66:792–795)

For many years, the standard 12-lead electrocardiogram has served as the primary clinical tool for diagnosing the presence and location of myocardial infarction. However, the traditional electrocardiographic criteria used to diagnose myocardial infarction have been proven to be relatively insensitive.[1-2] Subsequent studies[3-5] have proposed improved criteria to identify infarcts in the common locations of the left ventricle; inferior and anterior. However, some of these criteria require an electrocardiogram of exceptional technical quality and therefore may not be easily applied routinely.

Using computer simulations of the human heart activation sequence, Selvester et al[6,7] identified electrocardiographic changes that occur with various sizes of infarcts in the distributions of the 3 major coronary arteries. A complete 54-criteria/32-point QRS scoring system[8] was then developed to estimate infarct size. Each of these criteria has attained ≥95% specificity in normal subjects, but a score of >3 points was required to achieve that specificity standard for identifying the presence of an infarct. Thus, use of the complete scoring system in screening for myocardial infarction would be too insensitive to include small lesions in the range of 1 to 10% of the left ventricle. It therefore became necessary to identify a subset of 3 screening criteria[9] (Q wave ≥30 ms in lead aVF, any Q or R wave ≤10 ms and ≤0.1 mV in lead V_2, and R wave ≥40 ms in V_1) to detect single nonacute infarcts. Cumulatively, this subset achieved 95% specificity, and 84 and 77% sensitivities for inferior and anterior infarct groups, respectively, among patients identified by cardiac catheterization. However, these sensitivities have never been validated in anatomically proven infarcts or in any patients with multiple infarcts in which electrocardiographic signal cancellation of criteria for 1 infarct by another might potentially occur.[10,11] Using anatomically documented single and multiple infarct populations, the purpose of this study was to evaluate the sensitivity of these screening criteria for detecting infarcts in all locations of the left ventricle.

METHODS

Patient population: Deceased patients from 8 collaborating medical centers as previously described,[12-14] and the Multicenter Investigation of Limitation of Infarct Size group[15] were included if they had: (1) ≥1 anatomically identifiable infarct of the left ventricle,

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and (2) a postmyocardial infarction electrocardiogram with no confounding factors such as ventricular hypertrophy, bundle branch or fascicular block, or paced rhythm. The time interval between the last stable electrocardiogram and patients' deaths ranged from 1 to 300 days (mean 19). Patients were classified into inferior, anterior, posterolateral and multiple infarct groups according to anatomic infarct location as described later. Those with single infarcts constitute the same populations included in previous reports,[12-14] and infarct size ranged from 1 to 57% (mean 17%). Those with multiple infarcts were new cases collected during the latter part of the study and infarct size ranged from 3 to 48% (mean 23%).

Anatomic techniques: The hearts, collected between 1969 and 1988, were prepared and studied at the time of autopsy by previously described methods.[16,17] The heart was divided into inferior, anterior and posterolateral thirds, with a line from the centroid of the left ventricle to the midseptum serving as the reference line.[12-14] The divisions correspond approximately to the 3 major coronary artery distributions: left anterior descending, right and left circumflex. The greatest percent infarction in any third determined the location among patients with single infarcts. The multiple infarct group had ≥2 noncontiguous infarcts involving different coronary artery distributions.

Electrocardiographic techniques: The final "stable electrocardiogram" was identified for each patient. This electrocardiogram showed no evidence of electrolyte imbalance, pericarditis or cardiogenic shock. Table I lists the screening criteria. All measurements were obtained manually with hand-held calipers. Q and R durations were measured in milliseconds along the PR baseline (1 mm = 40 ms), and the R amplitude in millivolts (1 mm = 0.1 mV). The 3 screening criteria are referred to according to the lead in which each occurs.

Examples of the varieties of the wave forms are illustrated in Figure 1. The "aVF criterion" is met by a Q wave ≥30 ms either as QR (A1) or QS (A2) in the absence of any notches. A notched Q wave (A3) is present if there is reversal in direction of ≥0.05 mV within the initial negative deflection. In this instance, duration of the Q wave is measured along the PR segment baseline from the onset of the negative deflection to the point directly above the peak of the notch. The "V_2 criterion" is met either by a Q wave (B1) or the combined R wave ≤10 ms and ≤0.1 mV (B2) or both the Q and R components (B3). The "V_1 criterion" is met by an R wave ≥40 ms which may occur as Rs (C1), rS (C2) or simply as R (C3). More complex variations of these wave forms are seen in patients with multiple infarcts. Each electrocardiogram was then evaluated for the performance of the individual criteria occurring singly or in combination in all infarct locations.

TABLE I Screening Criteria for Nonacute Myocardial Infarcts

Lead	Screening Criteria
aVF	Q ≥30 ms
V_2	Any Q or R ≤10 ms and R ≤0.1 mV
V_1	R ≥40 ms

RESULTS

One hundred three patients were included in the study: 71 had single infarcts (30 inferior, 21 anterior and 20 posterolateral) and 32 had multiple infarcts. Seventy-seven (75%) were men (age range 28 to 78 years, mean 57) and 26 (25%) were women (age range 35 to 84 years, mean 63).

Table II summarizes the sensitivities of the screening criteria. Among patients with single inferior infarcts, the aVF criterion was present uniquely in 83% and in combination with one of the other criteria in an additional 7%. For patients with single anterior infarcts, the V_2 criterion was the only one met and it achieved a 67% sensitivity. In the single posterolateral infarct population, both the aVF and V_1 criteria achieved 20% unique

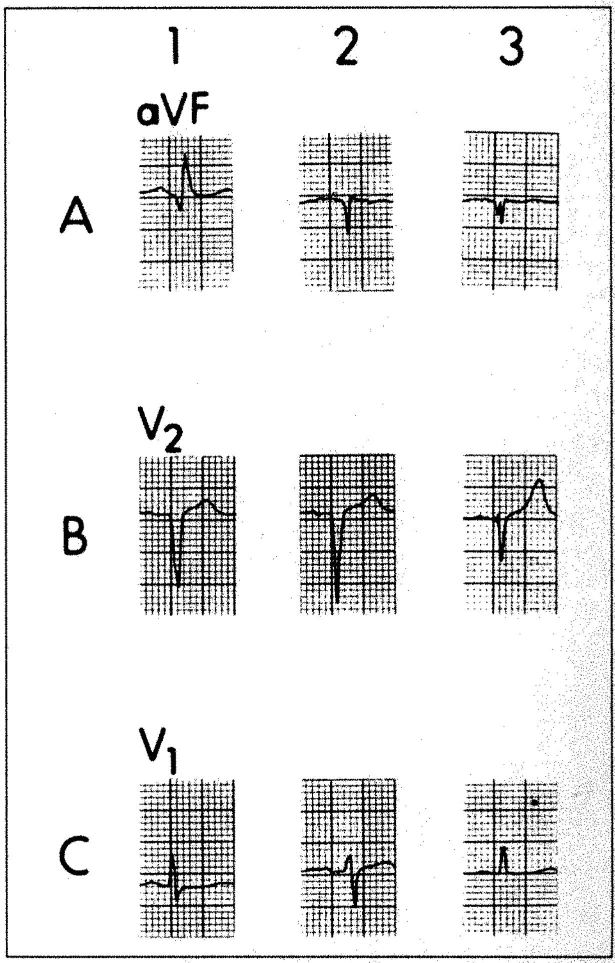

FIGURE 1. Varieties of wave forms of the screening criteria: *Panel A,* Q wave ≥30 ms aVF criterion occurring as QR (A1), QS (A2) or notched Q (A3); *panel B,* Q or R wave ≤10 ms and ≤0.1 mV V_2 criterion occurring as Q wave (B1), both minimal R components (B2), or combined Q and R components (B3); *panel C,* R wave ≥40 ms V_1 criterion occurring as Rs (C1), rS (C2), or R (C3).

TABLE II Sensitivities of Screening Criteria

	Anatomic Infarct Location				
	Single (n = 71)				
Screening Criteria	Inferior (n = 30)	Anterior (n = 21)	Posterolateral (n = 20)	Multiple (n = 32)	Total (n = 103)
aVF alone	83%	0	20%	41%	41%
V_2 alone	0	67%	0	3%	14%
V_1 alone	0	0	20%	3%	5%
aVF and V_2	0	0	0	25%	8%
aVF and V_1	7%	0	5%	0	3%
V_1 and V_2	0	0	0	0	0
Any	90%	67%	45%	72%	71%

sensitivities and an additional 5% was gained with combination of the aVF and V_1 criteria. Among patients with multiple infarcts, the aVF criterion had the highest unique sensitivity (41%) and the screening set achieved 72% sensitivity. The overall sensitivity of the screening set in the 103 patients in all 4 groups was 71%.

DISCUSSION

Traditional diagnostic criteria for myocardial infarction have been highly specific, but their low sensitivities have intensified the need to improve the ability of the electrocardiogram to identify infarcts in the different locations of the left ventricle. Many studies have focused on the inferior infarct location. Hurd et al[18] reported poor sensitivity (4 to 34%) by all 3 sets of traditionally strict electrocardiographic criteria that required both Q duration and amplitude components. Starr et al[1] developed improved vectorcardiographic criteria and compared their performance with the commonly used electrocardiographic criteria: Q wave $\geq$30 ms in aVF alone and the Q wave $\geq$30 ms in leads II, III and aVF. The vectorcardiographic criteria proved to be more sensitive (84%) than the Q wave in aVF alone (60%), or the Q wave in all 3 leads (28%). Subsequently, Warner et al[4] introduced new "contour criteria" based on the temporal relationships between the QRS complexes recorded simultaneously in leads II and III. The sensitivity increased over that achieved by the aVF Q wave $\geq$30 ms alone from 59 to 93%.

The results of the present study parallel those of previous reports. In the single inferior infarct group, the Q wave $\geq$30 ms in aVF was highly sensitive (90%). This higher sensitivity may be explained by the weakness of the method by which the previous studies defined inferior infarction. The use of coronary angiography and left ventriculography to identify patients with inferior infarcts has its limitations. Unlike the anatomic method, these can neither definitively identify the inferiorly located infarct nor exclude an infarct in other locations. Anatomic studies[17] demonstrated that akinesia or dyskinesia is usually associated with some amount of fibrosis but hypokinesia frequently is not associated with any fibrosis. Conversely normally contracting walls may contain as much as 25% fibrosis. These studies[1,4,9,18,19] used only qualitative methods to define the various degrees of wall motion abnormality, whereas the study comparing anatomy and ventriculography[17] demonstrated better correlations using quantitative methods.

For the anterior infarct group, Starr et al[2] found low sensitivity (43%) using traditional electrocardiographic criteria. Warner et al[5] systematically analyzed a large number of variables and identified the V_2 criterion of any Q wave or an initial R wave <20 ms as attaining highest sensitivity (83%). Hill et al[19] also reported excellent sensitivities using either this same V_2 criterion or the V_3 criterion of any Q or R wave <25 ms.

In the present study, the only criterion from the screening set met in the anterior infarct group was that of the Q or combined R amplitude and duration in V_2, which yielded 67% sensitivity. More lenient electrocardiographic criteria probably accounted for the higher sensitivity reported in previous studies. In the present study, both R duration and amplitude limits must be met, and the R duration limit is tighter than that of Warner et al[5] ($\leq$10 ms vs $\leq$20 ms). In considering the difficulty in manually differentiating 10 from 20 ms, an automated analysis system would be required to compare sensitivities of these 2 anterior infarction screening criteria.

No highly sensitive criterion has been developed to diagnose posterolateral infarction, and it is unlikely that any will be identified because of the variable arterial supply of the posterolateral myocardium. Huey et al[20] reported 21% sensitivity of the $\geq$40 ms R wave in V_1 or an R/S $\geq$1 in V_1 or V_2 in patients with infarcts in the left circumflex distribution. Perloff[21] proposed considering slurs or notches following the peak of the R wave in V_1. Sclarovsky et al[22] demonstrated that in consecutive patients with maximal ST-segment change appearing as depression in V_2 and V_3 the typical subsequent change was Q-wave development in "lateral" leads. The present study clearly shows that none of the 3 screening criteria are sensitive in identifying a posterolateral infarct. This result is not surprising since this set of screening criteria was not developed from a population with posterolateral infarct location. Since the criteria that have recently been added to the simplified Selvester scoring system (S $\leq$0.3 mV in V_1 and $\leq$0.4 mV in V_2) have proved useful in estimating the size of posterolateral infarcts,[23] a study is in progress to identify their value for screening for this location. It is also possible that by using nonstandard leads—that is, upper left precordial and left axillary leads, as suggested by others[24]—new posterolateral screening criteria could be developed.

This study is the first to test a set of myocardial infarction screening criteria in patients with multiple infarcts. Screening criteria could perform better for multiple than for single infarcts because >1 infarct is present, or poorer because of signal cancellation. Disappearance of electrocardiographic patterns of prior anterior infarction as a result of acute inferior infarction[10,11] or vice versa[25] has been reported. Such change was attributed to the loss of opposing electromotive forces in the region of the more recent infarct. The present study shows that the set of screening criteria performs just as well for multiple as it does for single infarcts.

The frequently accepted and easy to apply aVF criterion is exceptionally sensitive for screening for inferior infarct. Because no Q-wave criterion in any of the precordial leads is highly sensitive for anterior infarcts, some abnormal aspects of the V_2 R wave must also be considered for screening for this common location. Although much emphasis has been placed on the R wave duration, no "best definition" can be attained via manual measurement. An R amplitude criterion may prove most useful for manual screening. Entirely new criteria will be required to screen for posterolateral infarcts. The addition of new criteria for the anterior and posterolateral locations may improve screening for infarcts in multiple areas of the left ventricle as well.

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Two-Year Outcome After Angiographically Documented Myocardial Reperfusion for Acute Coronary Occlusion

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Reperfusion therapy has been clearly shown to decrease the early mortality after acute myocardial infarction, but the impact of this therapy on long-term survival has been less extensively evaluated. This study reports the extended follow-up of a large cohort of 810 patients treated with intravenous thrombolytic therapy combined, when considered necessary to maintain or augment infarct vessel patency, with mechanical reperfusion therapies. Each patient underwent coronary angiography within 2 hours of the initiation of the thrombolytic infusion. Coronary angioplasty was performed in 62% of the patients before hospital discharge and 21% underwent coronary artery bypass graft surgery. Follow-up was obtained in 96% to a mean of 18.8 months (range, 1.5 to 48 months). All-cause mortality over this period was 3.3%; 2.1% died from cardiac causes. Nonfatal reinfarction occurred in 5.1%. Although the low event rate limits the validity of statistical comparisons, the patients who survived the follow-up period tended to be younger (56 ± 10 vs 65 ± 7 years), to have better predischarge left ventricular function (left ventricular ejection fraction, 52 ± 11 vs 46 ± 13%) and to have a lower prevalence of multivessel coronary artery disease (45 vs 67%). This excellent long-term survival may, in part, reflect the exclusion of high-risk patients from enrollment in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) studies. It may also be attributable, however, to the frequent use of combined thrombolysis and mechanical revascularization in this population.

(Am J Cardiol 1990;66:796–801)

During the past 2 decades, the in-hospital mortality rate from acute myocardial infarction has decreased progressively. This has been due, firstly, to the impact of cardiac monitoring and the rapid treatment of cardiac arrhythmias and, secondly, to the shift in emphasis from therapeutic strategies aiming to decrease myocardial work and oxygen demand to therapies that actively restore myocardial oxygen supply. Several randomized, controlled trials have reported 30-day mortality rates ranging from 5.0 to 10.7%[1-4] after reperfusion therapy. This compares with early fatality rates of 16% for hospitalized men and 28% for women in the Framingham Study,[5] a study performed before the widespread use of antiplatelet and β-adrenergic blocking therapy and before the use of thrombolytic therapy, direct coronary angioplasty and emergency coronary artery bypass graft surgery.

Since January 1985, the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group has evaluated myocardial reperfusion strategies using intravenous thrombolysis and adjunctive medical therapies combined, when considered appropriate, with coronary angioplasty. The impact of these strategies on left ventricular functional recovery and on in-hospital mortality,[6-11] and the 1-year outcome of the 386 patients in the first TAMI study[12] have been previously reported. This study examines the clinical outcome over a more extended follow-up period of the larger cohort of patients enrolled in the first 4 TAMI studies.

METHODS

Patient selection: Between January 1985 and March 1988, 810 patients were enrolled in 4 phases of the TAMI study. The study protocols were similar for each phase and have been previously published.[7-11] Patients were eligible for enrollment if they presented within 6 hours of the onset of chest pain and had ≥0.1 mV ST-segment elevation in ≥2 contiguous electrocardiographic leads or ST-segment depression in the precordial leads consistent with posterior wall infarction. Patients were ineligible if they had contraindications to thrombolytic therapy, were ≥76 years of age, had a history of prior coronary artery bypass graft surgery or Q-wave myocardial infarction in the same territory as the acute event or were in cardiogenic shock (defined as a systolic blood pressure <85 mm Hg that was unresponsive to the administration of intravenous fluids).

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TABLE I Baseline Demographic and Angiographic Characteristics of the Hospital Survivors with Complete Follow-Up Data (n = 727)

Sex (% men)	82
Age (yrs)	56 ± 10
Risk factors (%)	
Diabetes mellitus	14%
Systemic hypertension	40%
Hyperlipidemia	12%
Cigarette smoking	65%
Vascular disease	
Cerebral	2%
Peripheral	5%
Time to therapy	176 ± 66 min
Infarct-related artery	
Left anterior descending	39%
Right coronary artery	48%
Left circumflex	12%
Other	0.3%
Acute angiography	
Left ventricular ejection fraction	51 ± 11%
Multivessel disease	45%

TABLE II Predischarge Treatment of Hospital Survivors with Complete Follow-Up

Thrombolytic agent	
Tissue plasminogen activator	69%
Urokinase	13%
Tissue plasminogen activator + urokinase	18%
Predischarge coronary angioplasty	
Acute	42%
Emergency	8%
Elective	25%
Predischarge coronary artery bypass surgery	
Emergency	6%
Urgent	6%
Elective	10%
Infarct vessel patency at discharge	
Patent (TIMI 2,3)	63%
Occluded (TIMI 0,1)	8%
Surgically bypassed	22%
Unknown	7%

TIMI = Thrombolysis in Myocardial Infarction trial.

Treatment regimen: The thrombolytic agents used were recombinant tissue plasminogen activator (tPA) and urokinase, given alone or in combination.[7-10] In 1 phase, tPA was combined with intravenous prostacyclin.[11] All patients received oral aspirin and intravenous heparin for ≥4 days after admission and the majority received intravenous nitroglycerin and prophylactic intravenous lidocaine. Oral diltiazem and β-adrenergic blocking agents were given as clinically indicated for hypertension, arrhythmias or recurrent myocardial ischemia. Cardiac catheterization was performed within 90 minutes of the initiation of the thrombolytic therapy to document baseline global and regional left ventricular function and to determine the patency status of the infarct vessel. Rescue angioplasty was performed if the infarct vessel remained occluded (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0 or 1). Patients with TIMI 2 or 3 flow in the infarct vessel and suitable anatomy were randomized in the first phase to either immediate or to deferred angioplasty of residual infarct vessel stenoses. In subsequent phases, angioplasty of the infarct vessel was performed acutely only if it remained occluded 90 minutes after the initiation of the thrombolytic therapy. Cardiac catheterization was repeated before hospital discharge to evaluate changes in global and regional left ventricular function and infarct vessel patency. Coronary angioplasty of residual stenoses in the infarct-related artery was performed at the time of the predischarge cardiac catheterization if submaximal exercise thallium testing showed evidence of reversible ischemia in the infarct territory and the coronary anatomy was deemed suitable for the procedure. Intercurrent coronary angiography was also performed for symptoms of recurrent myocardial ischemia or hemodynamic instability. Emergency coronary artery bypass graft surgery was performed for ongoing myocardial ischemia when the infarct vessel subserved a large myocardial territory and was either unsuitable for coronary angioplasty because of the presence of left main (or equivalent) coronary artery disease or extreme tortuosity or if patency of the infarct vessel could not be achieved and maintained after intravenous thrombolytic therapy and balloon dilatation.[13] Urgent coronary artery graft surgery was performed for recurrent myocardial ischemia and elective surgery for provocable ischemia when the coronary anatomy precluded coronary angioplasty.

Follow-up: Regular follow-up was performed after hospital discharge by telephone and mailed questionnaire. The events recorded included death, nonfatal myocardial infarction, functional class (Canadian Heart Association Classification) and postdischarge coronary angioplasty or coronary artery bypass graft surgery. The timing and cause of death were determined when possible by examination of death certificates and reports of postmortem studies. Events leading to rehospitalization were determined by the study nurse during follow-up contact and by examination of hospital records.

Statistics: All values are quoted as mean ± 1 standard deviation unless otherwise stated. A Kaplan-Meier estimate was used to construct a curve of long-term out-of-hospital survival. Statistical comparisons of baseline characteristics and outcomes between groups were not made because of the low event rate and the observational nature of the data.

RESULTS

Patient characteristics: Baseline characteristics of the patients surviving to hospital discharge are listed in Table I. The use of thrombolytic therapy, predischarge coronary angioplasty and bypass graft surgery, and the patency status of the infarct-related artery are listed in Table II. Of the 810 patients, 757 were discharged from the hospital alive. Follow-up has been obtained on 727 (96%) of these to a mean of 18.8 months (25th, 75th percentiles; 13.3, 24.4 months). The age of the patients surviving to hospital discharge was 56 ± 10 years; 82% were men. Mean predischarge global left ventricular ejection fraction was 51%; 25% of the patients had an

TABLE III Baseline Characteristics of Patients Alive at Last Follow-Up Compared with Non-Survivors.

	Survivors (n = 703)	Non-Survivors (n = 24)
Sex (% men)	82	79
Age (yrs)	56 ± 10	65 ± 7
Infarct vessel status at discharge		
Coronary artery bypass graft	22%	20%
TIMI 2 or 3	63%	67%
TIMI 0 or 1	8%	0%
Unknown	7%	13%
No. of diseased vessels (acute catheterization)		
0 to 1	55%	33%
2 to 3	45%	67%
Predischarge left ventricular ejection fraction	52 ± 11%	46 ± 13%

TIMI = Thrombolysis in Myocardial Infarction trial.

ejection fraction <43%. The infarct vessel was patent at discharge or had been surgically bypassed in 85%, was occluded in 8% and its status was unknown in the remaining 7%.

During the follow-up period, 24 deaths occurred. Figure 1 shows the survival curve, projected to 2 years, of patients discharged from the hospital alive. The cause of out-of-hospital death was cardiac in 15 patients (2.1%) and noncardiac, predominantly due to disseminated malignancy, in 9 patients (1.2%). Nonfatal recurrent myocardial infarction occurred in 5.1%, coronary angioplasty was performed after hospital discharge in 7.4% and 5.4% underwent elective coronary artery bypass graft surgery (Figure 2). Comparison of the patients surviving the follow-up period with the non-survivors (Table III) shows that there was no apparent difference in sex distributions or infarct vessel patency status between the 2 groups. However, the non-survivors tended to be older, to have worse left ventricular function and more extensive coronary artery disease. Subgroup analysis of out-of-hospital events according to the patency status of the infarct-related artery is listed in Table IV. Surprisingly, no deaths were recorded in the group of 54 patients with non-patent infarct vessels. The mortality rate for patients with patent infarct vessels was 3% and for those with unknown patency status was 5%.

DISCUSSION

The principal finding of this study is that an aggressive strategy of early intravenous thrombolysis combined with mechanical revascularization for residual or

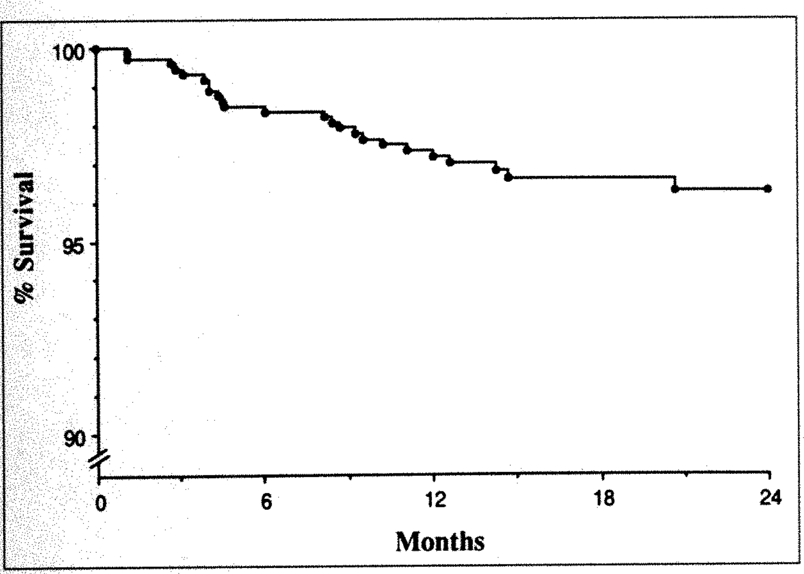

FIGURE 1. Kaplan-Meier survival curve for patients discharged from hospital alive (n = 757).

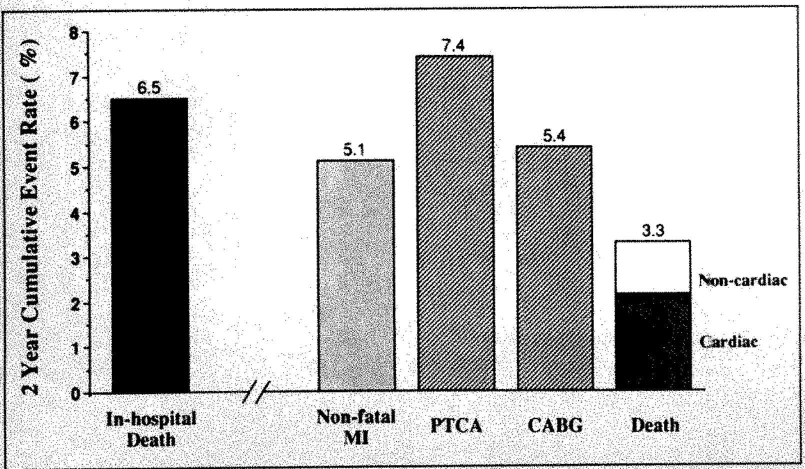

FIGURE 2. Bar graphs showing in-hospital mortality for total population (n = 810), and out-of-hospital mortality, nonfatal reinfarction rate and need for revascularization procedures during follow-up period in population of hospital survivors (n = 757). CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

TABLE IV Baseline Characteristics and Outcome According to Patency of Infarct-Related Artery (IRA) at Hospital Discharge

	Patent IRA (n = 610)	Non-Patent IRA (n = 58)	Unknown Status (n = 57)
Sex (% men)	83	84	68
Age (yrs)	56 ± 10	55 ± 9	54 ± 11
Left ventricular ejection fraction			
Acute (%)	51 ± 11	55 ± 10	49 ± 13
Day 7 (%)	52 ± 11	52 ± 10	51 ± 14
Infarct zone regional wall motion			
Acute (SD/chord)	−2.56 ± 1.07	−2.59 ± 1.00	−2.36 ± 1.21
Day 7 (SD/chord)	−2.12 ± 1.24	−2.69 ± 1.05	−2.02 ± 1.26
Events after discharge (%)			
Death	3	0	5
Nonfatal myocardial infarction	5	9	2
Coronary angioplasty	8	6	7
Coronary artery bypass surgery	5	13	4
Time to follow-up (months) (mean ± SD)	19 ± 8	20 ± 8	18 ± 7

SD = standard deviation.

recurrent myocardial ischemia was associated with excellent long-term survival and a low incidence of late recurrent ischemic events. A progressive decline in the incidence of death from coronary artery disease has been documented over the past 2 decades[5,14,15] and has been attributed to both the primary prevention of coronary artery disease and a decrease in periinfarction mortality.[14,15] Our results suggest that early reperfusion therapy has not only further decreased periinfarction mortality but has also substantially improved long-term postinfarction survival. The patients in this study do represent a relatively low-risk cohort since elderly patients, those in cardiogenic shock and patients presenting late after the onset of their symptoms were excluded from enrollment. Nonetheless, the out-of-hospital survival of this TAMI population compares favorably with that of similar cohorts of patients treated with less aggressive therapeutic regimens.

Mortality after thrombolysis: Two large, placebo-controlled thrombolytic trials have used conservative postlytic strategies. In the Gruppo Italiano per lo Studio della streptochinasi nell'infarto miocardico (GISSI) study,[16] streptokinase therapy was associated with a 10% decrease in cumulative 1-year mortality from 19.0 to 17.2% ($p = 0.008$). The decrease in mortality was particularly striking for patients treated within 1 hour of the onset of symptoms (12.9 vs 21.2%, $p = 0.00001$, relative risk = 0.6). A similar decrease in cumulative 2-year mortality was noted in each subgroup of the second International Study of Infarct Survival (ISIS-2),[2] from 19.0% in the control group to 13.5% in the group receiving streptokinase and aspirin. In both studies, the survival curve of the patients treated with thrombolytic therapy paralleled that of the respective control groups suggesting that the principal impact of thrombolytic therapy on survival occurred during the acute, hospital phase.

Combined pharmacologic and mechanical reperfusion therapy: In contrast to the above 2 trials in which predischarge coronary angioplasty or bypass graft surgery were rarely performed, the TAMI study protocol evaluated a strategy of intravenous thrombolysis, acute-phase coronary angiography and, in a large proportion of the patient population, urgent coronary angioplasty and/or coronary artery bypass surgery. Elective revascularization procedures were also performed in a relatively high proportion of the patients before hospital discharge. This strategy has the theoretical advantages of maximizing infarct vessel patency and the extent of myocardial salvage, of decreasing the likelihood of infarct vessel reocclusion and reinfarction, and of preserving function of the non-infarct zone in patients with multivessel disease. Using this intensive revascularization strategy, the out-of-hospital mortality in this study was only 3.3% at a mean follow-up of 18.8 months, with a cardiovascular mortality of 2.1%. The incidence of nonfatal reinfarction was 5.1% which is comparable to that of other studies.[16–18] Similar postlytic strategies were used by Stack[19] and Kander[20] and their colleagues. The 1-year survival was 94% in the former study and, in the latter, the 2-year survival was 93.6% and correlated with infarct vessel patency, left ventricular ejection fraction and the absence of prior myocardial infarction. Comparable 1-year survival rates have also been reported after direct coronary angioplasty.[21]

Three randomized trials have directly compared an "invasive" postlytic revascularization strategy with a more conservative approach.[22–24] Cumulative 1-year mortality was 6.9% in the invasive group of the TIMI 2B study compared with 7.5% in the conservative group.[22] It should be noted, however, that elective revascularization procedures were performed in a relatively high proportion of the conservative strategy group (37%) during the follow-up period. Low 90-day mortality rates have also been reported for both groups of the "Should We Intervene Following Thrombolysis?" trial (3.2 vs 4.8%).[23] Patients enrolled in this study were ≤70 years old, presented within 3 hours of the onset of symptoms of their first myocardial infarction and required 24 hours of clinical stability to be eligible for randomization. Thus, they also represent a low-risk population and any difference in long-term survival between the 2 postlytic strategies is likely to be small. In the European Cooperative Study,[24] 1-year mortality was actually somewhat higher after tPA with immediate PTCA (9.6%) compared with thrombolysis alone (5.5%) but the difference did not reach statistical significance.

Surgical reperfusion: Perhaps the most direct method of rapidly achieving myocardial revascularization is by emergency coronary artery bypass graft surgery. A long-term study of surgical reperfusion therapy for acute myocardial infarction was recently reported by DeWood et al.[25] When compared with a similar group of patients treated with conventional medical therapy, the overall 13-year actuarial mortality rate was significantly decreased (27 vs 41%, $p = 0.0007$).

Mechanisms of improved survival after reperfusion therapy: Several mechanisms are likely to contribute to the improved survival after reperfusion therapy. Patency of the infarct-related artery has been associated with significant improvement in long-term survival even in the absence of an improvement in left ventricular function.[19,26-28] Possible explanations for this observation include a decreased incidence of left ventricular aneurysm formation independent of the extent of myocardial salvage,[29] greater electrical stability of the injured myocardium,[30,31] a decrease in left ventricular mural thrombus formation[32] and the provision of a conduit for later recruitment of a collateral vascular supply to the contralateral myocardium. Somewhat surprisingly, in this study there were no deaths during the follow-up period in the group of patients discharged from hospital with an occluded infarct vessel. In comparison, although they had significantly better regional infarct zone wall motion and an improvement rather than deterioration in global left ventricular function, the group with patent infarct-related arteries had a 3% mortality. The cause of this discrepancy is unclear. One final mechanism should be considered. It has been suggested[33] that the improved out-of-hospital survival in patients treated aggressively may be due to the accelerated and premature death of high-risk patients before hospital discharge. In this study, however, the overall in-hospital mortality was only 6.5% which is comparable to that of other large thrombolytic trials including those with conservative postthrombolysis protocols.

Study limitations: All long-term follow-up studies are limited by incomplete data collection and the possibility of underreporting of event rates during the follow-up period. The survival status of 30 patients of the original cohort discharged from hospital is unknown. Theoretically, therefore, the actual mortality rate could be as high as 7%. This problem is not unique to this study and the 96% follow-up obtained is comparable to that achieved in other large, multicenter studies. A second limitation is the absence of a control population that may have permitted more definite conclusions about the value of this therapeutic approach. Finally, conclusions drawn from this study cannot be applied to the large proportion of the myocardial infarction population excluded from eligibility from this trial because of advanced age, late presentation or contraindications to thrombolysis. Further systematic evaluation is required to better define optimal treatment strategies and the prognosis for long-term postinfarction survival of these important groups of patients.

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Functional Significance of Myocardial Perfusion Defects Induced by Dipyridamole Using Thallium-201 Single-Photon Emission Computed Tomography and Two-Dimensional Echocardiography

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The mechanisms responsible for inhomogeneous myocardial blood flow after oral administration of a large dose (300 mg) of dipyridamole were assessed in 27 patients with serial thallium-201 single-photon emission computed tomography (SPECT) and simultaneous 2-dimensional echocardiograms. Myocardial tomographic images were obtained 50 minutes and 3 to 4 hours after administration of dipyridamole. Two-dimensional echocardiograms were recorded at baseline and then every 15 minutes for 60 minutes. Dipyridamole caused only a mild reduction in blood pressure (from 129 ± 18 to 126 ± 16 mm Hg) and a mild increase in heart rate (from 69 ± 15 to 73 ± 4 beats/min).

Sixteen patients had perfusion defects after dipyridamole by SPECT, which underwent partial or total filling-in. Fourteen of these patients (87.5%) had either a new abnormality or further deterioration of a preexisting wall motion abnormality by 2-dimensional echocardiography, and thus were considered to have developed transient ischemia during dipyridamole administration. Ten of 11 patients (91%) with normal perfusion or fixed defects by SPECT had no further deterioration in wall motion after oral dipyridamole, and were thus considered to have no evidence of myocardial ischemia.

In conclusion, most patients with transient thallium-201 defects after dipyridamole develop transient worsening of resting wall motion by 2-dimensional echocardiography, suggestive of true myocardial ischemia. Because myocardial oxygen demand, as indicated by the heart rate–blood pressure product, did not change significantly, the mechanism of myocardial ischemia in these patients is likely to be diminished regional blood flow related to a "subendocardial steal" induced by dipyridamole.

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Thallium-201 myocardial imaging after exercise has been widely used in the detection of coronary artery disease. Dipyridamole has also been used in combination with thallium-201 imaging to uncover areas of myocardial hypoperfusion, as an alternative approach to exercise stress.[1-7] Dipyridamole is a potent vasodilator with relatively selective effects on the coronary resistance bed.[8-12] During maximal pharmacologic coronary dilatation, coronary blood flow increases predominantly in the normally perfused myocardial regions. Therefore, during pharmacologic hyperemia, normally perfused myocardium will accumulate more thallium-201 than the myocardium supplied by stenotic arteries, which will show relative hypoperfusion. Although this hypoperfusion does not necessarily result from myocardial ischemia, many patients develop typical anginal pain after dipyridamole, and some even develop ischemic electrocardiographic changes, raising the possibility that myocardial ischemia does indeed occur.[13] This has been attributed to "myocardial steal."[14]

To gain insight into the mechanisms of inhomogeneous myocardial blood flow after dipyridamole administration, we performed serial thallium-201 single-photon emission computed tomography (SPECT) to evaluate myocardial blood flow distribution, and simultaneous 2-dimensional echocardiography to assess regional left ventricular wall motion. Transient wall motion abnormalities induced by dipyridamole were considered to represent segmental myocardial ischemia. Serial recordings of heart rate and blood pressure were used to estimate changes in myocardial oxygen demand.

METHODS

Twenty-seven patients with angina pectoris underwent thallium-201 SPECT and simultaneous 2-dimensional echocardiography after orally administered dipyridamole. All patients had a history of stable, exertional angina and 14 patients had a history of remote myocardial infarction. Nineteen of 27 patients (70%) were taking cardiac medications: 4 were taking β blockers, 13 were taking calcium channel antagonists, and 16 were taking long-acting nitrates. None of the patients was taking methylxanthines. Coronary angiography was performed within 48 hours of the thallium-201 dipyridamole–SPECT imaging in all but 4 patients, who did not undergo angiography. The severity of coronary artery

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narrowing was expressed as percent area stenosis, determined from caliper measurements of traced coronary artery silhouettes in 2 orthogonal projections. Significant area stenosis was defined as ≥70% narrowing in ≥1 of the major epicardial coronary arteries.

Study protocol: Patients fasted on the day of the study, receiving only their medications with sips of water. An intravenous infusion of 5% glucose in water was administered through an arm vein. Twelve-lead electrocardiograms, blood pressures and heart rates were recorded at baseline and then every 15 minutes for 1 hour.

All patients received 300 mg of dipyridamole tablets, which had been crushed and mixed with 100 ml of water immediately before ingestion. The patients then rested in the laboratory under constant supervision for 40 minutes, followed by ambulation about the room for 5 minutes. Three millicuries of thallium-201 were injected through the venous cannula and flushed with the 5% glucose solution. Two-dimensional echocardiograms were recorded at baseline, before dipyridamole administration, and every 15 minutes for 1 hour after dipyridamole. Aminophylline (50 to 150 mg) was administered intravenously in patients who developed angina after dipyridamole, but only after ≥5 minutes had elapsed since the thallium injection and after the 2-dimensional echocardiographic images had been completed.

SPECT imaging: SPECT was performed using a rotating gamma camera (ADAC ARC-3000) with a low-energy, high-resolution, parallel-hole collimator interfaced to a computer (ADAC 3300), as previously reported from our laboratory.[4,15] Imaging commenced 5 minutes after the thallium-201 injection. An arc of 180° was used, spanning from the 45° left posterior oblique projection to the 45° right anterior oblique position. The images were acquired at 6° intervals for 40 seconds per image on a 64 × 64 × 8 byte matrix. Delayed "redistribution" images were obtained 3 to 4 hours later.

Transaxial reconstruction was done using a standard back projection technique with a Butterworth (order:5) filter and a 50% cutoff applied to the images. Reconstructed tomographic slices were reoriented in the short, horizontal long, and vertical long axes, and displayed sequentially on a large color oscilloscope for visual interpretation.

Interpretation of thallium-201 SPECT images: The myocardial segments were visually analyzed in the short, horizontal long and vertical long axes. These segments were matched according to the coronary artery distribution as follows: septal and anterior segments corresponded to the left anterior descending artery; inferior and posterior segments to the right coronary artery; and lateral segments to the circumflex artery. The apex did not define any particular vessel distribution.

An image was considered abnormal if there was a decrease, by visual inspection, of thallium-201 uptake in any of the segments listed previously. The presence or absence of redistribution was noted. Tomographic images were interpreted by consensus of 3 investigators who had no knowledge of the coronary arteriographic findings.

Two-dimensional echocardiography: All 2-dimensional echocardiograms were recorded by an experienced echocardiographer in the standard parasternal long, short-axis and apical 2 and 4 chamber views with the patient in the left lateral decubitus position. The optimal echocardiographic windows were marked on the patient's chest and subsequent echocardiograms were repeated from these positions every 15 minutes for 1 hour and at the onset of chest pain. The images were stored on videotape (VHS format, ½″) for subsequent analysis.

Selected echocardiographic images were digitized in an off-line analysis station (Microsonics CAD 886AT) and displayed on a 4-quadrant screen, using a continuous cine loop format. The loop consisted of 16 frames at 33-ms intervals which could be played continuously at varying playback speeds. The resting image was displayed in the left upper quadrant, and the 15-minute image in the right upper quadrant. The subsequent images were placed in the left and right lower quadrants. For each time sequence, the physician reviewed the videotape and selected a single high-quality cardiac cycle from each view for storage in digital format. The procedure was repeated for each view.

The images were interpreted by an experienced echocardiographer unaware of the patient's clinical history, coronary anatomy or the dipyridamole thallium-201 SPECT imaging results. Side-by-side comparison of baseline and subsequent images allowed detection of subtle wall motion abnormalities. The free wall of the left ventricle was divided into anterior, lateral, posterior and inferior walls, and the septum into inferior and anterior segments. Each of the walls and the septum were subdivided into basilar, mid- and apical segments. Each segment was graded as normal, hypokinetic, akinetic or dyskinetic using previously validated criteria.[16] Development of a new wall motion abnormality was defined as ischemia, worsening of a wall motion abnormality present at baseline was considered ischemia plus scar, and abnormal wall motion at baseline that did not change further during dipyridamole was considered scar.

Statistical analysis: Changes in blood pressure and heart rate were analyzed by paired *t* tests. A p value <0.05 was considered significant. Data are expressed as mean ± standard deviation.

RESULTS

Coronary angiography: All patients were studied because of angina pectoris. One-vessel coronary disease was present in 15 of the 23 patients who had coronary angiography (65%) and involved the right coronary artery in 7 cases, the left anterior descending in 6 cases, and the left circumflex artery in 2 cases. Two-vessel disease involving the left anterior descending and the right coronary arteries occurred in 3 patients, and 3-vessel disease in 4 patients. One patient had insignificant coronary stenoses.

Hemodynamic effects of dipyridamole: Dipyridamole caused only a slight decrease in blood pressure, from 129 ± 18 to 126 ± 16 mm Hg (difference not significant), and a minimal increase in heart rate, from 69 ± 15 to 73 ± 11 beats/min (difference not significant). Myocardial oxygen demand, as inferred by rate-pressure product, was unchanged.

TABLE I Correlation of Perfusion Defects and Wall Motion Abnormalities

	Tl-201 SPECT		2-D Echocardiography	
Case	Affected Walls	Defect Type	Affected Walls	Type of Abnormality
1	Septal	I	Anterior	I
2	Inferior/posterior	I	Inferior/distal septal	I + S
3	Septal/apical	I	Anterior/lateral/septal/apical	I + S
4	Inferior/posterior	I	Inferior/posterior	I + S
5	Anteroseptal	I	Normal	
6	Inferior/posterior/lateral	I	Inferior	I + S
7	Inferior/posterior	I	Inferior/septal	I + S
8	Inferior/posterior/lateral	I + S	Posterior	I
9	Anterior/lateral/septal	I + S	Diffuse	I + S
10	Septal/apical	I + S	Septal/apical	S
11	Inferior/posterior	I + S	Inferior/posterior	I + S
12	Inferior/posterior	I + S	Inferior/posterior	S
13	Inferior/posterior/apical/lateral	I + S	Inferior/posterior/lateral	I + S
14	Anterior/septal/apical	I + S	Inferior	S
15	Inferior/posterior	I + S	Inferior/posterior	I + S
16	Inferior/posterior/lateral	I + S	Inferior/posterior/lateral	I + S
17	Inferior/posterior	S	Inferior/posterior	S
18	Apical	S	Normal	
19	Apical	S	Anterior/lateral/apical	S
20	Inferior/posterior	S	Inferior/posterior	S
21	Normal		Normal	
22	Normal		Normal	
23	Normal		Normal	
24	Normal		Normal	
25	Normal		Normal	
26	Normal		Normal	
27	Normal		Inferior/posterior	S

2-D = two-dimensional; I = ischemia, I + S = ischemia and scar, S = scar.

Thallium-201 SPECT: Twenty patients (74%) had abnormal perfusion scans. Perfusion defects were totally reversible in 7 patients, partially reversible in 9 patients and fixed in 4 patients.

Relation between perfusion defects and occurrence of angina and electrocardiographic changes after dipyridamole: Angina occurred in 10 patients after dipyridamole administration. Eight of the 10 patients with chest pain had a reversible perfusion defect, 1 had a fixed defect and another had no perfusion defects by thallium SPECT imaging. Six patients had electrocardiographic changes suggestive of myocardial ischemia (≥1 mm horizontal or downsloping ST-segment depression, measured at 0.08 second after the J point). Five of these patients demonstrated reversible perfusion defects, and 1 patient had a fixed perfusion defect.

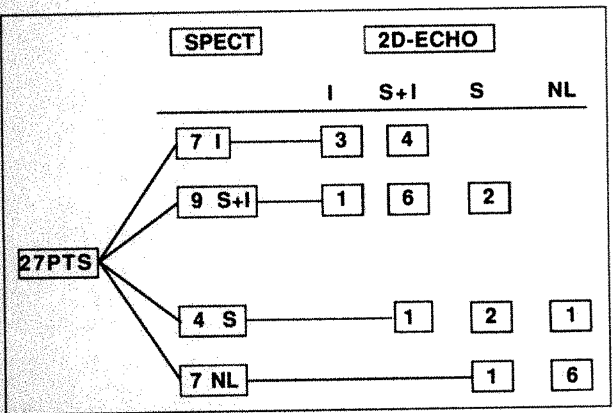

FIGURE 1. Correlation of 2-dimensional echocardiograms (2D-ECHO) and single-photon emission computed tomography (SPECT) in the 7 patients with transient perfusion defects (I), 9 patients with defects with partial filling-in (S + I), 4 patients with fixed defects (S) and 7 patients with normal (NL) SPECT. The echocardiographic definition of ischemia (I), scar and ischemia (S + I) or scar (S) are detailed in the text.

Comparison of thallium-201 SPECT with two-dimensional echocardiography: The perfusion defects observed with thallium-201 SPECT and the wall motion abnormalities by 2-dimensional echocardiography always involved myocardial segments in the same vascular distribution, except in the few cases detailed later (Table I). All 7 patients who demonstrated totally reversible defects by SPECT also had evidence of ischemia by echocardiography (Figure 1). Three patients had a new wall motion abnormality, and 4 had worsening of a preexisting resting wall motion abnormality. An example of a patient with reversible perfusion and wall motion abnormalities is shown in Figure 2. Of the 9 patients who demonstrated partially reversible perfusion defects, 1 had a new wall motion abnormality, 6 had worsening of a preexisting wall motion abnormality and 2 had a segmental wall motion abnormality at rest that was unchanged after dipyridamole. Of the 4 patients with fixed defects by SPECT, 2 had a baseline wall motion abnormality that remained unchanged, 1 had worsening of a preexisting wall motion abnormality, and 1 had a normal echocardiographic study. Six patients with normal SPECT images were also normal by 2-dimensional echocardiography. Two of these 6 patients who had coronary angiography were found to have noncritical coronary disease. One patient with normal SPECT images had a baseline posterior wall abnormality by echocardiography that remained unchanged after dipyridamole. This patient had a 90% stenosis of the distal right coronary artery.

Thus, a total of 16 patients had perfusion abnormalities by SPECT imaging that demonstrated partial or complete redistribution. Fourteen of these patients (87.5%) had evidence of ischemia defined as a new wall motion abnormality or worsening of resting wall motion abnormality by echocardiography.

DISCUSSION

Frequency of myocardial ischemia after dipyridamole: To demonstrate whether myocardial ischemia occurs in association with perfusion defects induced by dipyridamole, we performed thallium-201 SPECT and 2-dimensional echocardiography in 27 patients with angina pectoris. We chose to administer dipyridamole orally because the intravenous formulation is not yet approved by the Food and Drug Administration. Previous investigators have demonstrated similar mean blood levels of dipyridamole after intravenous or oral administration.[3] Furthermore, our own previous experience with Tl-201 SPECT during oral dipyridamole administration has shown excellent sensitivity and specificity in the diagnosis of coronary artery disease.[4] In the present investigation, we observed new or worsening of preexisting regional wall motion abnormalities in 14 of 16 patients with partially or totally reversible perfusion defects. Thus, myocardial ischemia occurred in most (87.5%) of the patients with reversible perfusion defects by thallium-201 SPECT. Further corroborative evidence indicating the presence of myocardial ischemia was the development of typical angina after dipyridamole in 10 patients, 8 of whom had reversible perfusion defects and

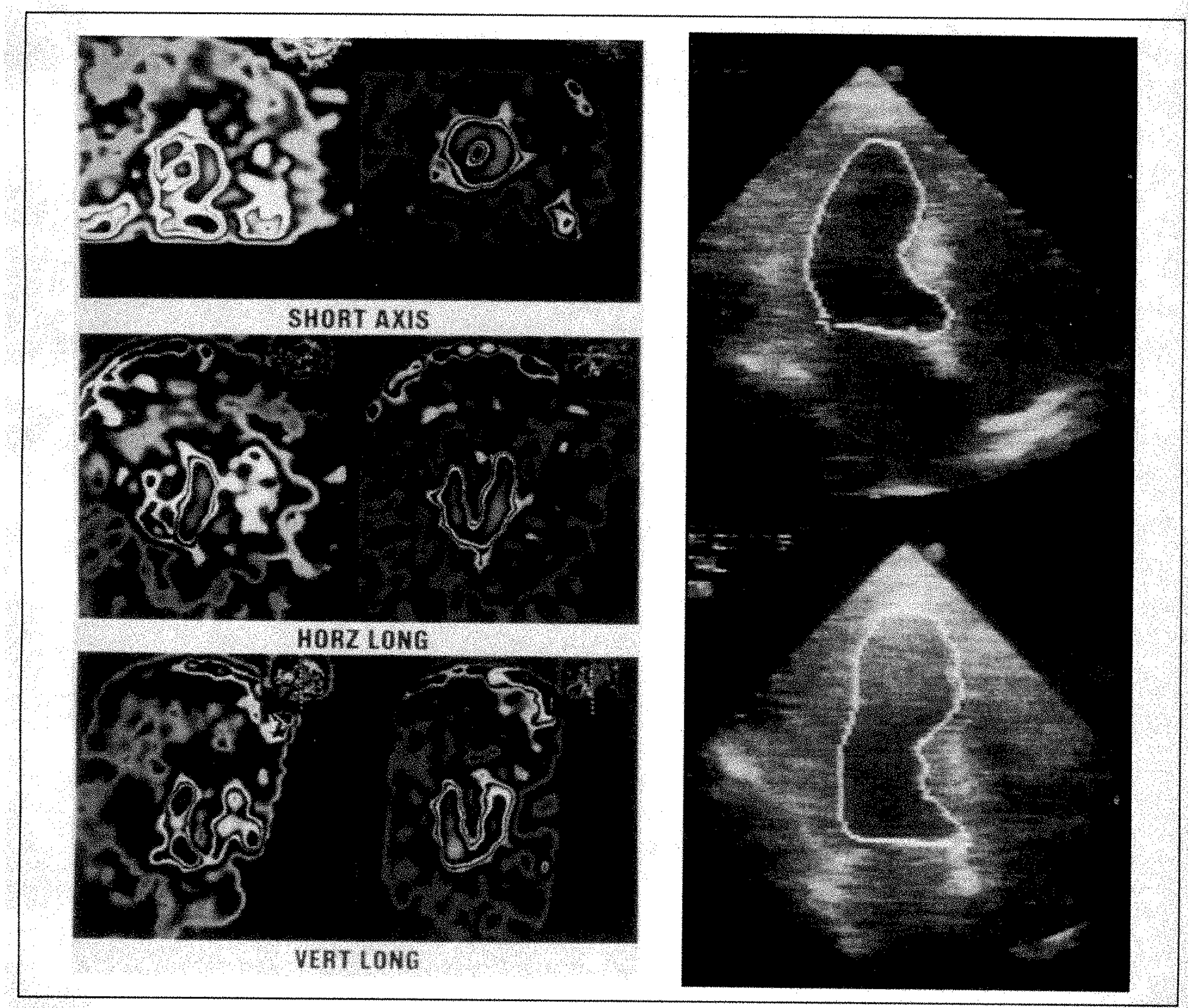

FIGURE 2. ***Left,*** **midcavity slices during dipyridamole (images on the *left*) and during redistribution (images on the *right*). Perfusion defects are apparent in the anterior wall, septum, apex and posterior wall during dipyridamole and fill-in during the redistribution images. In the short axis, the anterior is at the top, posterior at the bottom, septum on the left and lateral wall on the right. In the horizontal long axis, the septum in on the left, the apex at the bottom and the lateral wall on the right. In the vertical long axis, the anterior wall is on the left, the apex at the bottom, and the posterior wall on the right. Horz long = horizontal long axis; Vert long = vertical long axis.** ***Right,*** **end-systolic 2-dimensional echocardiographic frames (4-chamber view) in the same patient shown at left during baseline *(upper panel)* and after dipyridamole *(lower panel)*. Septal and apical akinesis were observed during dipyridamole. These frames show the apex at the top, the lateral wall on the left, and the septum on the right.**

new wall motion abnormalities. Only 2 patients with partial redistribution on their perfusion defects had no evidence of ischemia by 2-dimensional echocardiography. Both of these patients had baseline wall motion abnormalities that did not deteriorate further after dipyridamole.

Mechanism of transient perfusion defects and ischemia induced by dipyridamole: Dipyridamole is a potent coronary vasodilator that significantly increases blood flow to myocardium perfused by normal coronary arteries.[8-12,18] The flow increase is considerably less in the vascular bed of a stenosed artery, resulting in areas of heterogeneous myocardial thallium-201 uptake, thus allowing identification of coronary artery disease.

Because myocardial oxygen demand, estimated from the heart rate–systolic blood pressure product, did not change significantly in our patients, the mechanism of ischemia was most likely a redistribution of blood flow, with a decrease in subendocardial perfusion.[17-19]

The finding of frequent reversible wall motion abnormalities induced by dipyridamole strongly supports segmental myocardial ischemia as an important factor in the genesis of perfusion defects after dipyridamole.

Previous studies with dipyridamole and echocardiography: Recent studies[20,21] using echocardiography have also demonstrated wall motion abnormalities after intravenous infusion of dipyridamole, with a sensitivity for detecting coronary artery disease ranging from 50 to 80%. Although these studies have not included assessment of myocardial perfusion, their findings support the concept of ischemia produced by a steal phenomenon.

Recently, Labovitz et al[22] performed Doppler and 2-dimensional echocardiography in patients undergoing planar thallium-201 scintigraphy after intravenous dipyridamole administration. They observed good agreement between perfusion and wall motion in normal or abnormal segments, although they did not report whether these abnormalities were reversible. Thus, these investigators did not address the issue of mechanisms of the perfusion defects.

Study limitations: Several limitations exist in our investigation. The number of patients studied was relatively small and the interpretation of both the echocardiograms and SPECT images was qualitative. This type of analysis, however, is still the most frequently used in most centers across the country. The techniques employed to assess coronary blood flow distribution and regional ventricular function do not have perfect sensitivity, and it is possible that small areas with either perfusion or wall motion abnormality were missed. Nonetheless, this possibility does not invalidate our findings. In fact, the good correlation observed between the segments with reversible hypoperfusion and wall motion abnormalities lends support to the concept that both are clinically useful techniques to assess the effects of dipyridamole on coronary circulation.

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Left Ventricular Dilatation and Pulmonary Thallium Uptake After Single-Photon Emission Computer Tomography Using Thallium-201 During Adenosine-Induced Coronary Hyperemia

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This study examined the implications of left ventricular (LV) dilatation and increased pulmonary thallium uptake during adenosine-induced coronary hyperemia. The lung-to-heart thallium ratio in the initial images was significantly higher in patients with coronary artery disease (CAD) than normal subjects; 0.48 ± 0.16 in 3-vessel disease ($n = 16$), 0.43 ± 0.10 in 2-vessel disease ($n = 20$), 0.43 ± 0.08 in 1-vessel disease ($n = 16$) and 0.36 ± 0.05 in normal subjects ($n = 7$) ($p < 0.001$, 0.09 and 0.06, respectively). There was a significant correlation between the severity and the extent of the perfusion abnormality (determined from the polar maps) and the lung-to-heart thallium ratio ($r = 0.51$ and 0.52, respectively, $p < 0.0002$). There was also a significant correlation between lung thallium washout and lung-to-heart thallium ratio ($r = 0.42$, $p = 0.0009$) and peak heart rate ($r = -0.49$, $p < 0.0001$). The LV dilatation was mostly due to an increase in cavity dimension (30% increase) and to a lesser extent (6% increase) due to increase in LV size. (The cavity dimensions were measured from the short-axis slices at the midventricular level in the initial and delayed images.) The dilation was seen in patients with CAD but not in the normal subjects. These changes correlated with the extent and severity of the thallium perfusion abnormality. Thus, adenosine-induced coronary hyperemia may cause LV dilation and increased lung thallium uptake on the basis of subendocardial ischemia.

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Thallium-201 myocardial imaging during coronary vasodilatation with dipyridamole has been extensively investigated. The results have proven to be of value in the diagnosis of coronary artery disease (CAD) and in risk stratification.[1-4] We and others have recently described the use of thallium-201 imaging during coronary vasodilatation with adenosine; a very short acting (half-life <10 seconds) powerful coronary vasodilator.[5,6]

Previous studies have shown that increased pulmonary thallium uptake and left ventricular (LV) dilation during exercise are markers of extensive CAD.[7-11] The purposes of this study were, therefore, to examine the implications of increased pulmonary thallium uptake and LV dilatation during adenosine thallium studies.

METHODS

Patient population: There were 59 patients in this study, 7 with normal coronary angiograms, and 52 with CAD defined as ≥50% diameter stenosis of ≥1 major coronary artery. All patients were being evaluated for chest pain, and both the coronary angiographic and adenosine thallium studies were done within 1 month of each other. All patients signed a consent form approved by the institutional review board of the medical center. The protocol and the results of the imaging have previously been published and will be summarized below.[5] Based on the results of coronary angiography, 16 patients had 1-vessel disease, 20 patients had 2-vessel disease and 16 patients had 3-vessel disease. The pertinent demographic data in these patients are listed in Table I. No patient had actue myocardial infarction within 1 week, rest angina pectoris or active bronchospastic disorder and none were on theophylline-containing medications.

Adenosine protocol: Antianginal medications were withheld on the morning of the test. Intravenous infusion of adenosine (Adenoscan™ Medco Research, Inc.) was initiated at a dose of 0.14 mg/kg/min using an infusion pump and continued for a total of 6 minutes. At the end of the third minute of infusion, a dose of 3.5 mCi thallium-201 was injected intravenously. The heart rate, blood pressure and electrocardiogram were recorded at baseline and during each minute of infusion and for 5 minutes during recovery. Thallium images were obtained 5 minutes and 4 hours after thallium injection.

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TABLE I The Pertinent Demographic Data on Patient Population

Age (yrs)	62 ± 10
Men/women	38/21
Q-wave myocardial infarction	22 (37%)
Medications	
Nitrates	36 (61%)
β blockers	21 (36%)
Calcium antagonists	37 (63%)
Chest pain during test	21 (36%)
ST depression during adenosine infusion	5 (8%)

Single-photon emission computed tomography with thallium-201: Our method for SPECT thallium studies has previously been described.[12] Images are acquired using a circular orbit over 180° arc starting at the 45° right anterior oblique projection and ending at the 45° left posterior oblique projection. Each of 32 projections are acquired using a 64 × 64 matrix at 40 seconds/image. Each projection is corrected for nonuniformity using a 30 million count Co-57 flood. Standard filtered-back projection technique is applied using a Ramp-Hanning filter with a cutoff frequency of 0.83 cycles/cm to generate transaxial slices. No scatter or attenuation correction is used. From these transaxial images, the long axis of the left ventricle is identified and the oblique angle images are generated in the short-axis, vertical long-axis and horizontal long-axis orientations.

Maximal counts circumferential profiles are generated on each of the short-axis slices in forty 9° arcs and ranging from apex to base.[13] These count profiles are then interpolated to the equivalent of 15 slices and stored in two 15 × 40 arrays, 1 for the stress and 1 for the delayed distribution. For display purposes, these arrays are then transformed into polar plot known as the "raw bull's-eye map." In order to identify stress perfusion defects objectively, each patient's profiles are compared to gender-matched normal files developed from the low likelihood of CAD. Previously, it was established that profile curves representing 2.5 standard deviations below the mean normal values as the threshold for stress perfusion defect detection. The cluster profile points falling below this established normal limit are identified as the extent of the defect. Subsequently, these abnormal points are transformed to polar coordinates and plotted in a blacked-out bull's-eye in which the black region within the bull's-eye plot defines the extent of the stress perfusion abnormality.[13]

The extent of the perfusion abnormality is estimated as the percentage of the total area and the severity score was derived from the extent and the number of standard deviations below the mean normal for each point within the abnormal area.

Pulmonary thallium uptake: Two regions of interest were drawn, 1 over the left lung, and the second over the LV myocardium in the anterior projection using a 40-second acquisition frame. Count densities were derived in both initial and 4-hour delayed images. The lung-to-heart thallium uptake ratio was measured from the initial images and the lung thallium washout was expressed as (initial lung counts − delayed counts)/initial counts × 100 (Figure 1).

Left ventricular dilatation: For the purpose of this analysis, a short-axis slice at the mid-LV level was used in both initial and delayed images. The diameter of the LV cavity was measured by a caliber as the distance between the inner borders of the myocardium. The total LV diameter was measured as the distance between the outer borders of the LV myocardium. The area of the LV cavity and the total LV area (which includes the cavity plus the myocardium) were measured assuming that both areas are circular in shape (Area = $\pi \times [\text{diameter}/2]^2$).

The reasons for these measurements were based on the assumption that changes in LV cavity size may be due to either myocardial thinning due to subendocardial ischemia or due to increase in LV size. Special care was

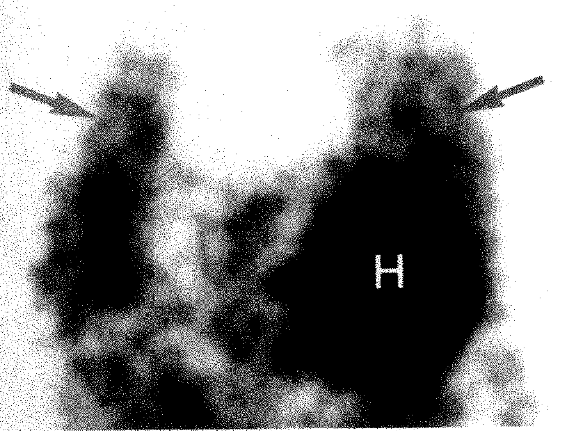

FIGURE 1. Thallium images in anterior projection showing increased lung thallium uptake *(arrows)* in one of the patients. H = heart.

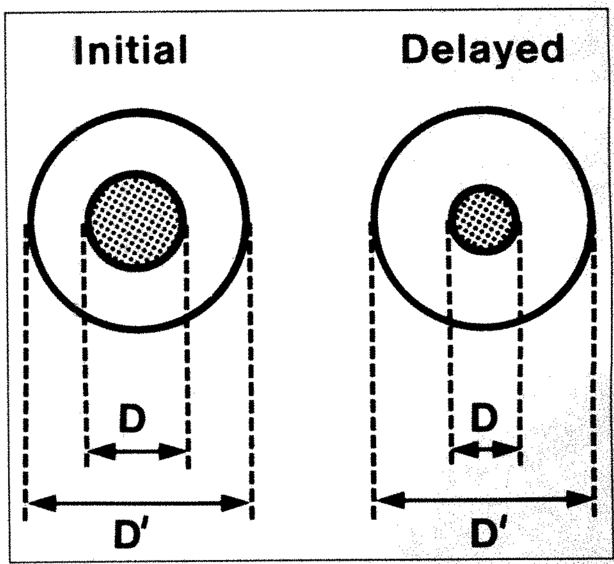

FIGURE 2. Schematic representation of method for measuring left ventricular dilation. D = inner diameter; D' = outer diameter.

taken to obtain the measurements at identical slices in the initial and delayed images (Figure 2). Changes in LV cavity and total area were expressed as (initial area − delayed area)/delayed area × 100. The intraobserver variability in measuring the LV dimension, myocardial and pulmonary thallium uptake was small; r = 0.93, 0.99 and 0.82, respectively ($p < 0.0001$, n = 20).

Statistical analysis: Data are presented as mean ± standard deviation (SD) when appropriate. The chi-square and Student's *t* test were used for comparison. Linear regression analysis was used to estimate the relative agreement between 2 variables. A probability value <0.05 was considered statistically significant.

RESULTS

Hemodynamic responses: The heart rate increased from a mean of 68 ± 2 beats/min at baseline to 87 ± 18 beats/min at peak infusion ($p < 0.0001$). There was a slight but significant increase in double product during adenosine infusion (9.2 vs 12.0 × 10^3 beats/min · mm Hg, $p < 0.0001$).

Side effects: These have been detailed elsewhere.[5] In general, side effects were transient and of mild nature. In only 3 patients, termination of adenosine infusion or treatment with aminophylline were necessary. The side effects included headaches, flushing, chest pains and nausea.

There was a slight but significant increase in the PR interval from 0.17 ± 0.02 to 0.19 ± 0.03 second during adenosine infusion ($p < 0.001$); 8 patients developed first-degree atrioventricular block but none had second- or third-degree block.

Results of adenosine single-photon emission computed tomography thallium-201 imaging: The sensitivity and specificity were 94 and 100%, respectively. Thus, the images were normal in the 7 patients with normal coronary angiograms and were abnormal in 49 of the 52 patients with CAD (Figure 3). These results were previously reported.[6] Only 1 of the 60 original patients was not included in this analysis because the delayed images were deleted from our databank. The severity thallium score was 125 ± 126 in normal subjects and 552 ± 460 in patients with CAD ($p < 0.001$) and the extent score was 5.6 ± 5.3% in normal subjects and 17.4 ± 10.5% in patients with CAD ($p < 0.005$).

Pulmonary thallium uptake: The initial lung-to-heart thallium ratio was significantly higher in patients with CAD than normal subjects; 0.48 ± 0.16 in 3-vessel disease, 0.43 ± 0.10 in 2-vessel disease, 0.43 ± 0.08 in 1-vessel disease and 0.36 ± 0.05 in normal subjects ($p < 0.001$, 0.09 and 0.06, respectively). The lung-to-heart ratio in this study was lower than that reported by others using exercise studies.[12] We, however, used SPECT rather than planar imaging and adenosine rather than exercise.

There was a significant correlation between the thallium severity and extent scores and the initial lung-to-heart thallium ratio (r = 0.51, and 0.52, respectively, $p < 0.0001$, Figure 4).

The lung thallium washout was 27 ± 9% in normal subjects and 29 ± 9% in patients with CAD. There was a significant correlation between the lung thallium washout and the lung-to-heart thallium ratio (r = 0.42, $p < 0.0009$) and with the peak heart rate (r = −0.49, $p < 0.0001$, Figure 5). The patients with CAD and increased lung thallium uptake (>1 SD above the mean in normal subjects; n = 28), had larger thallium extent score (21 ± 10 vs 14 ± 10%, $p < 0.01$) and thallium severity score (687 ± 436 vs 410 ± 442, $p < 0.03$) than the remaining patients with normal lung thallium uptake.

Left ventricular dilatation: In patients with CAD, there was a significant increase in the initial, compared to the delayed total LV size (38 ± 13 vs 36 ± 11 cm^2, $p < 0.003$) and inner cavity area (7 ± 5 vs 5 ± 4 cm^2, $p < 0.0001$). The percent change in inner cavity area was more than the percent change in total area (30 vs 6%, $p < 0.0001$). In contrast, in normal subjects, there were no

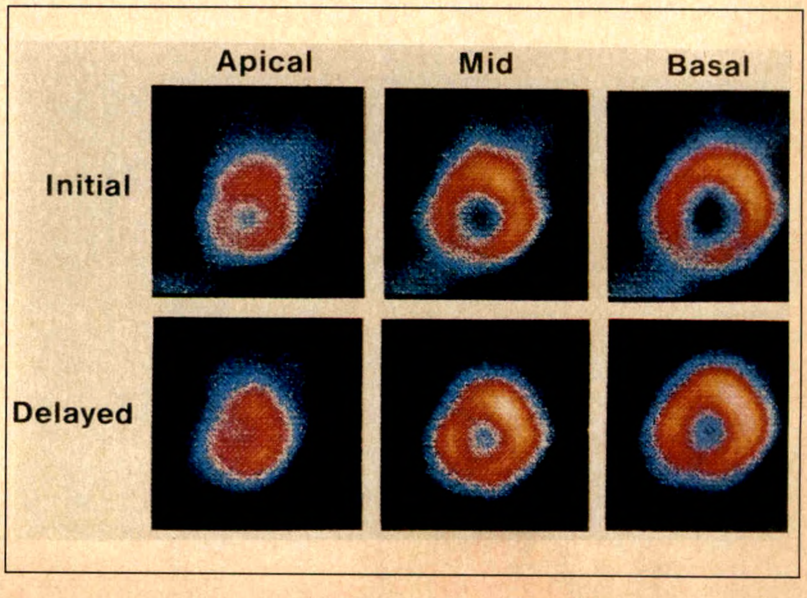

FIGURE 3. Initial and delayed single photon emission computed tomography thallium images during adenosine-induced coronary hyperemia obtained in the short-axis plane. There are reversible defects involving the septum and inferior wall with left ventricular dilation *(top panel)*.

significant changes in either total or inner cavity areas (initial inner area 3 ± 1 cm^2, delayed inner area 3 ± 1 cm^2, initial total area 32 ± 3 cm^2, delayed total area 30 ± 3 cm^2). There were significant correlations between LV size and the extent score ($r = 0.61$ for total area, and $r = 0.66$ for cavity size, $p < 0.0001$ each), and between LV size and severity score ($r = 0.72$ for total area and $r = 0.75$ for cavity size, $p < 0.0001$ each).

DISCUSSION

The main conclusions of this study are: first, increased lung thallium uptake may be seen in patients with CAD during adenosine-induced hyperemia; the uptake is related to the extent of the thallium abnormality; and second, LV dilatation during adenosine-induced coronary hyperemia is mostly due to myocardial thinning and subendocardial ischemia resulting in an increase in the cavity size with little change in the total LV size. The correlation between thallium extent score and lung-to-heart ratio is not a very strong one. A possible explanation is that the score represents scar and ischemia; it may be that having scar would not increase the LV filling pressure consequent to adenosine infusion. In other words, diastolic dysfunction is more likely to occur when the defects represent ischemia.

In a previous report on the same cohort of patients, we observed that most patients with CAD had perfusion defects during adenosine-induced hyperemia.[5]

We have postulated that most perfusion defects during adenosine or dipyridamole-induced coronary vasodilatation reflect heterogeneity in regional coronary blood flow.[5,14]

Consistent with this hypothesis is the low prevalence of ST-segment depression and regional wall motion abnormality. If, however, ischemia is not indeed present, then why should patients with CAD have increased lung thallium uptake? The answer may be that perfusion defects may represent ischemia that is subendocardial in location and therefore not easily detected. The ischemia may be explained by a modest increase in demand, transmural coronary steal, and intracoronary steal.[15] The failure to detect wall motion abnormalities may be related to the fact that a given thickness of the myocardium needs to be involved before wall motion abnormality can be detected. Alternatively, it is possible that visual assessment of wall motion abnormality may not be

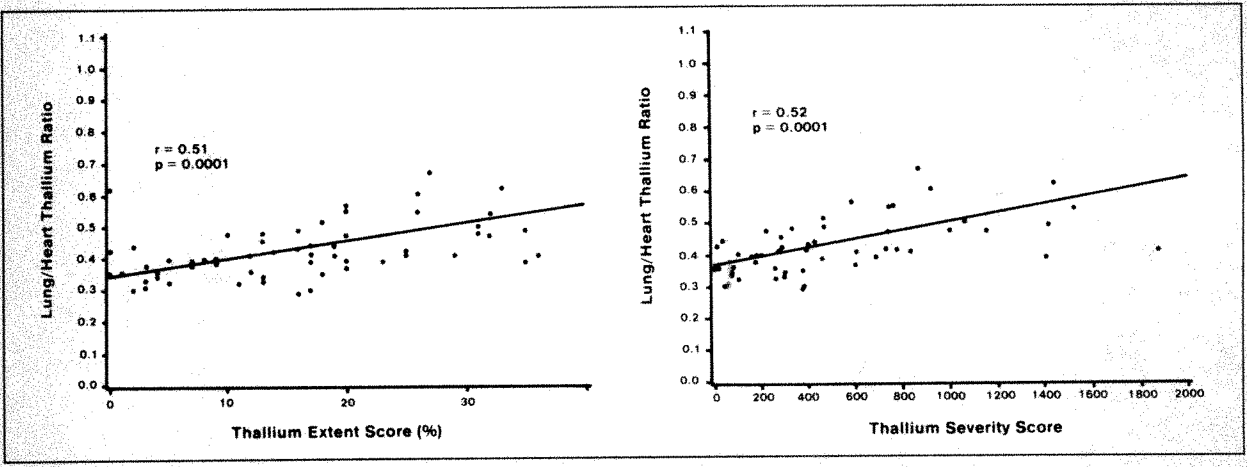

FIGURE 4. The relation between lung thallium uptake and severity and extent of thallium abnormality.

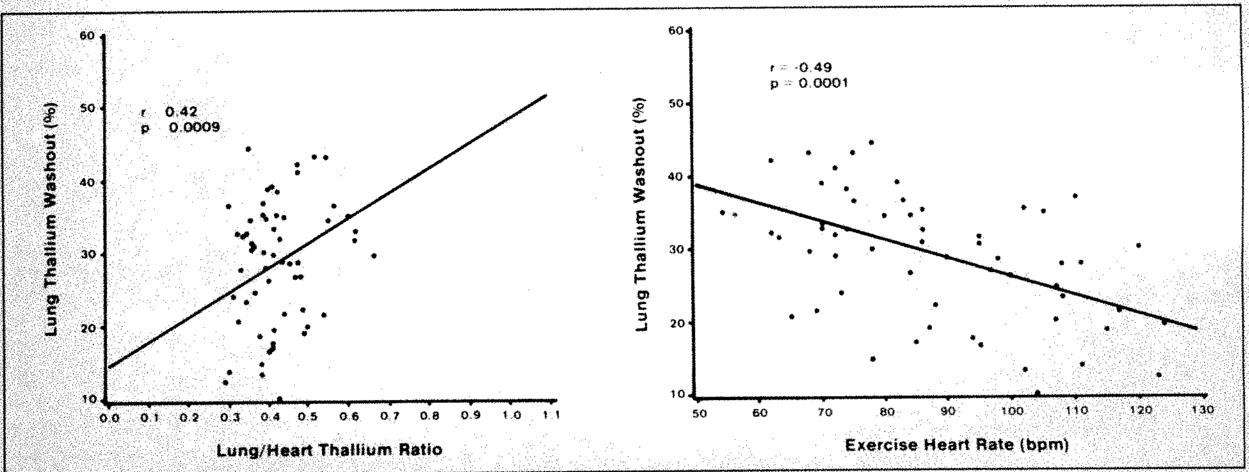

FIGURE 5. The relation between lung thallium washout and initial lung thallium uptake and peak heart rate.

reliable if the changes are of a mild degree. Furthermore, Picano et al[16,17] consistently reported higher prevalence of wall motion abnormality during dipyridamole echocardiographic studies. The dose of dipyridamole used by these investigators is, however, roughly 50% higher than the conventional dose and it is not clear whether wall motion abnormality and hence coronary steal is dose-dependent.

Consistent with the possibility of subendocardial ischemia is the mode of LV dilatation which, as described in this study, reflects myocardial thinning rather than true increase in LV dimension as seen during exercise studies, which is due to the use of the Frank-Starling mechanism. One should note, however, that SPECT images take approximately 25 to 30 minutes to complete from the time of adenosine injection and it is possible that true dilatation may have occurred but was transient and resolved by the time the images were completed.[18]

Both increased lung thallium uptake and LV dilatation similar to our results have been described by others using dipyridamole imaging.[7-11] However, our report is the first to describe these changes using adenosine as a coronary vasodilator. In our study, as with previous exercise studies, the increased lung thallium uptake and the LV dilatation were associated with more extensive thallium perfusion abnormalities.

The thallium washout rate during adenosine-induced coronary vasodilatation was consistent with previous studies. The washout rate is lower than that seen during exercise studies.[1] As shown in Figure 5, there is considerable overlap between lung-to-heart ratio and lung thallium washout, which suggests that the washout rate is not a clinically useful index.

As with exercise, the lung thallium uptake showed inverse relation to peak heart rate; a slower heart rate increases the extraction fraction across the pulmonary parenchyma.[19]

We selected patients with angiographic documentation of coronary disease and used SPECT imaging on all patients. The lung uptake was defined from regions of interest over the lung and the heart, and the LV size was assessed by a caliber from the short axis slice at the mid-LV level, 1 experienced observer did all measurements and the reproducibility data were quite good. Finally, the thallium abnormality was assessed quantitatively using an automated method based on polar map analysis. However, it is possible that LV dilatation may not be homogeneous and thus may not be reflected at the midlevel, and further studies with 3-dimensional quantitation may allow a better assessment of the volume changes.

Our imaging technique, as with other noninvasive techniques, does not allow detection of transmural changes in flow, and therefore our hypothesis about subendocardial ischemia must remain speculative, but is supported by prior animal experiments showing preservation of the reserve mechanism in the subepicardial, but not in the subendocardial layer in the presence of severe coronary stenosis.[15] Finally, an index that uses the variables of the lung-to-heart ratio, redistribution score and change in LV cavity dimension might be the best correlate of ultimate prognosis. This, however, requires further studies.

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Effects of Bepridil and Diltiazem on Ventricular Repolarization in Angina Pectoris

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Gilbert Motté, MD, and Patrice Jaillon, MD

To examine the time-course and potential predictors of prolongation of ventricular repolarization with the calcium antagonist bepridil, the effects of bepridil (300 to 500 mg/day; n = 45) and diltiazem (180 to 300 mg/day; n = 42) on QT and QTc interval duration were analyzed in a randomized double-blind study in patients with angina pectoris. Electrocardiograms were recorded before and 14, 28, 70 and 112 days after treatment was begun. After 14 days, bepridil prolonged QT interval by 26 ± 35 ms (range, −60 to 120 ms) and QTc (Bazett's formula) by 17 ± 33 ms (range, −73 to 107 ms) compared to baseline (both $p < 0.05$). QT or QTc did not significantly increase thereafter. However, among the 30 patients who had <40 ms QTc prolongation at day 14 compared with baseline, 13 (43%) exceeded this limit on at least 1 of the following visits. Diltiazem did not significantly alter QT or QTc intervals. The absolute change in QTc interval from baseline observed after 14 days of bepridil therapy was inversely proportional to the baseline QTc interval ($r = -0.68$; $n = 42$; $p < 0.001$). The degree of bepridil-induced QTc prolongation on day 14 correlated with pretreatment RR interval ($r = 0.36$; $n = 42$; $p < 0.02$). In conclusion, chronic administration of bepridil but not of diltiazem prolongs ventricular repolarization in patients with angina pectoris. The overall effects of bepridil therapy on QT and QTc intervals can be assessed by an electrocardiogram recorded after 14 days of treatment but subsequent measurements may be required in individual patients. A short baseline QTc interval and a slow initial heart rate may be potentially useful predictors of a greater QTc prolongation with bepridil.

(Am J Cardiol 1990;66:812–817)

The calcium antagonist bepridil hydrochloride,[1] β- [(2-methylpropoxy) - methyl] - N - phenyl-N - (phenylmethyl)-1-pyrrolidine-ethanamine monohydrochloride monohydrate, is a new investigational drug in the United States but has been available for the treatment of angina pectoris in Europe since 1981. In addition to its calcium channel blocking properties in cardiac and vascular tissues,[2] bepridil inhibits the fast sodium channel[2,3] and prolongs action potential duration[4] in cardiac cells. In humans these electrophysiologic properties are associated with beneficial effects of bepridil therapy in patients with angina pectoris[5] and a potential usefulness in the treatment of ventricular and supraventricular arrhythmias.[6-8]

Major concern arose about bepridil with the report of cases of torsades de pointes occurring during its administration.[9,10] Although the frequency of this arrhythmia is considered to be rare in view of the large use of the drug in Europe, it remains a qualitatively major adverse effect due to its potential lethality. In most patients, excessive prolongation of the QT interval is required for classic torsades de pointes to occur.[11] However, some degree of QT interval prolongation is a normal electrocardiographic feature during bepridil therapy[6,7] and during administration of any drug with Vaughan-Williams class III activity.[12] There is unfortunately no means to predict those individuals at risk of excessive QT prolongation during administration of a drug with class III activity. Some insight might be gained by analyzing the dynamics of QT prolongation (i.e., its time course and its relation to heart rate and baseline characteristics) during treatment with a QT-prolonging drug.

The multicenter bepridil-diltiazem study was a prospective, randomized, double-blind, parallel-groups study designed to assess the tolerance and persistent antianginal efficacy of these 2 calcium channel antagonists during a 4-month administration in patients with stable angina pectoris. We now report an ancillary study whose objective was to analyze the dynamics of the effects of bepridil and diltiazem on ventricular repolarization.

METHODS

Patients and treatments: Patients of both sexes with confirmed coronary artery disease and stable angina pectoris were asked to participate in each of the 39 centers (see Appendix) after giving their informed consent. Patients were not included if any of the following characteristics was found: previous history of ventricular arrhythmia; >1,440 ventricular ectopic depolarizations on

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a 24-hour ambulatory recording; age >70; uncompensated cardiac insufficiency; renal or hepatic insufficiency; sinus node disease or atrial flutter; amiodarone therapy within the last 4 months; resting heart rate <55 beats/min; QT interval >480 ms; second or third degree atrioventricular block; complete right or left bundle branch block or a combination of incomplete right and left anterior or posterior hemiblock; plasma potassium <3.8 mmol/liter or calcium <2.25 mmol/liter. Nitrates, molsidomine, digitalis, diuretics and potassium supplementation could be continued after randomization, but antiarrhythmic agents, calcium antagonists, β-adrenergic receptor antagonists, drugs prolonging QT, tricyclic antidepressants and neuroleptics had to be discontinued at the time of randomization.

Patients were randomly assigned to receive either bepridil or diltiazem in a double-blind manner. Patients were followed for 16 weeks after randomization with visits 14, 28, 70 and 112 days after beginning of therapy. The initial dosages of bepridil and diltiazem were 100 mg every 8 hours and 60 mg every 8 hours, respectively. Dosage could be titrated upward after 14 and 28 days if angina pectoris persisted, provided that QT interval remained <500 ms and PR interval was <280 ms. If needed, an additional 100 mg dose of bepridil or 60 mg dose of diltiazem was administered each day after the visit on days 14 and 28. The maximum dose of bepridil was 500 mg/day. The maximum dose of diltiazem was 300 mg/day. Patients were withdrawn during follow-up if angina pectoris persisted after administration of the maximum dose, if treatment was poorly tolerated hemodynamically, if ventricular arrhythmia developed, if plasma potassium was <3.4 mmol/liter or if QT interval increased to >500 ms. The protocol was approved by the ethics committee at 1 of the participating university hospitals.

In the main study, 227 patients were randomized to receive either bepridil (n = 116) or diltiazem therapy (n = 111). Of these 227 patients, 87 (38%) were free of bepridil, diltiazem and QT-prolonging drugs at the time of randomization. Of these, 45 were randomized to bepridil and 42 to diltiazem therapy. The present report is based on this subpopulation, for which analysis of ventricular repolarization is unbiased by previous treatment administered at the time of randomization (i.e., at baseline).

Electrocardiographic recordings and measurements. A baseline 12-lead electrocardiogram was recorded, just before randomization and 14, 28, 70 and 112 days after beginning treatment. Each electrocardiogram was recorded at a paper speed of 25 mm/s after a 15-minute period of rest in the supine position. All QT and RR intervals were measured in lead V_1 to V_3 by averaging 3 to 6 individual measurements. QT interval was measured from the onset of the Q wave to the end of the T wave. The U wave, when present, was excluded from measurements. RR interval was measured from the peak of an R wave to the peak of the following R wave. Electrocardiographic intervals were measured by 2 different investigators who were blinded to the patient's treatment. The final QT and RR intervals were obtained by averaging the 2 values measured by each investigator. To take into account the fact that QT depends on the heart rate at which it is measured, a corrected QT interval, QTc, was calculated as $QTc = QT \cdot (\sqrt{RR})^{-1}$, where RR is expressed in seconds.

TABLE I Baseline Characteristics of the Study Population

	Bepridil (n = 45)	Diltiazem (n = 42)
Sex (M/F)	37/8	33/9
Age (yrs)	58 ± 8	60 ± 7
Electrocardiographic features (ms)*		
QT interval	394 ± 27	396 ± 36
RR interval	884 ± 140	918 ± 190
QTc interval	422 ± 31	417 ± 28
Concomitant drug therapy		
Diuretic	6	9
β blocker†	17	13
None	12	13

There was no statistically significant difference between the 2 groups.
* Mean ± SD; † β-blockers were discontinued immediately after randomization.

Data analysis: EFFECT OF TREATMENTS ON QT, QTc AND RR INTERVALS: Values of QT, QTc and RR intervals during each treatment were compared over time by using general linear model analysis of variance. If the probability of erroneously rejecting the null hypothesis of no difference was <0.05, Duncan's post hoc test was performed to compare electrocardiographic intervals at different times under each treatment.[13] In this study, we considered QT or QTc intervals to be long if they were >440 ms. We also considered a prolongation of QTc interval to be clinically significant if the change from baseline was >40 ms. The number of patients having a QT or QTc interval of >440 ms and ≤440 ms at each visit was compared using contingency table analysis. The same approach was used to compare the number of patients achieving >40 ms and ≤40 ms of QTc prolongation from baseline during treatment.

CHANGE IN QT INTERVAL WITH HEART RATE: To assess whether a given treatment alters the relation between the absolute change in QT interval from baseline and the absolute change in RR interval from baseline on all follow-up visits, this relation was analyzed by least square linear regression. The 2 regression curves were compared according to the method of Altman and Gardner.[14]

PREDICTORS OF QTc CHANGES WITH BEPRIDIL: To determine whether the extent of drug-induced QTc prolongation, if any, depends on baseline QTc and RR intervals, we correlated the absolute change of QTc interval observed during treatment with the corresponding baseline QTc and RR interval in each patient. Since analysis of the change in a given parameter as a function of its baseline value is prone to statistical error,[15] we also correlated the absolute value of QTc interval during treatment with its pretreatment value.[16] In such an analysis, a slope different from unity would indicate that, on average, the change in QTc interval with treatment depends on the initial QTc interval.

RESULTS

Baseline characteristics of the patients were similar in the bepridil and the diltiazem group (Table I). The

TABLE II Effects of Bepridil on Ventricular Repolarization: Percentage of Patients Reaching Various End Points

	Baseline (n = 45)	Day 14 (n = 42)	Day 28 (n = 43)	Day 70 (n = 42)	Day 112 (n = 43)
QT >440 ms	4%	19%*	26%*	21%*	21%*
QTc >440 ms	22%	52%*	65%*	45%*	53%*
>40 ms increase in QTc from baseline	—	25%*	25%*	25%*	25%*

* p <0.05 vs baseline.

dose of bepridil was increased from 300 to 400 mg/day on day 14 in 2 patients and again to 500 mg/day on day 28 in 1 patient. The dose of diltiazem was increased from 180 to 240 mg/day on day 14 in 6 patients and again to 300 mg/day on day 28 in 1 patient. A total of 10 patients (2 bepridil; 8 diltiazem) dropped out of the study for non-cardiovascular reasons during follow-up. One patient in the diltiazem group was excluded on day 28 because of the appearance of >1,440 ventricular extrasystoles/day.

Effect of treatments on QT, QTc and RR intervals: Bepridil, but not diltiazem, prolonged QT interval and QTc interval (Figure 1). QT interval increased from (mean ± standard deviation) 394 ± 27 ms (range, 360 to 480 ms) at baseline to 421 ± 33 ms (range, 370 to 510 ms) on day 14 (p <0.05). Corresponding values for QTc interval were 422 ± 31 ms (range, 360 to 516 ms) and 442 ± 26 ms (range, 398 to 512 ms) (p <0.05). This increase in QT and QTc intervals with bepridil persisted during subsequent visits. There was, however, no significant increase in the mean degree of QT or QTc interval prolongation after day 14 (Figure 1). Compared to baseline, the proportion of patients in the group receiving bepridil who had a QT or QTc interval of >440 ms increased after 14 days of treatment and remained stable thereafter (Table II). Likewise, approximately 25% of patients treated with bepridil achieved >40 ms QTc prolongation compared to the pretreatment value at each of the follow-up visits (Table II). However, among the 30 patients who had <40 ms QTc prolongation on day 14 compared with baseline, 13 (43%) exceeded this limit on at least 1 of the following visits. QTc interval once reached a value of 500 ms in 11 of the 45 patients (24%) treated with bepridil. Only once was this limit attained on day 14. Pretreatment QTc values were significantly greater in these 11 patients (440 ± 30 ms; range, 398 to 516 ms) than in the 34 patients in whom QTc values never reached 500 ms (417 ± 30 ms; range, 360 to 490 ms) (p <0.04). Finally, neither bepridil nor diltiazem significantly altered RR interval (i.e., heart rate) (Figure 1). There was no torsades de pointes during follow-up in any patient.

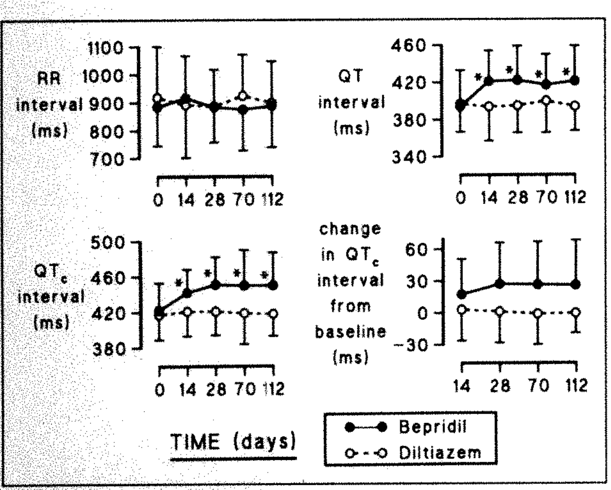

FIGURE 1. Effect of bepridil and diltiazem on the electrocardiogram at various times of followup. Means and standards deviations are represented for RR interval *(top left)*, QT interval *(top right)*, QTc interval *(bottom left)* and the change in QTc from baseline *(bottom right)*. *p <0.05 versus baseline.

Change in QT interval with heart rate: A significant relation between the absolute change in QT interval from baseline and the absolute change in RR interval from baseline on all follow-up visits was found with both bepridil and diltiazem (Figure 2). While the slope of the 2 regression curves did not differ significantly, the intercept of the regression curve was greater during bepridil therapy than during diltiazem therapy (p <0.05).

Predictors of QTc changes with bepridil: There was an inverse correlation between the absolute change in QTc interval from baseline on day 14 and the baseline QTc interval (Figure 3). This result was confirmed by the fact that the slope of the relation between QTc interval duration on day 14 and initial QTc interval duration was inferior to unity (slope, 0.27; 95% confidence interval: 0.025 to 0.525) (Figure 3). Similar results were found when the analysis was performed on data from all follow-up visits. Thus, bepridil tended to prolong QTc interval more in patients with short baseline QTc intervals than in those with comparatively long QTc intervals.

The absolute change in QTc interval from baseline on day 14 was proportional to the RR interval before bepridil therapy (Figure 4). There was a significant trend for bepridil to produce more QTc interval prolongation when administered to a patient with a relative pretreatment bradycardia than when administered to a patient with comparatively rapid heart rate.

DISCUSSION

The results of the present study confirm that bepridil prolongs ventricular repolarization in man.[4,6–8] The fact that the calcium channel antagonist diltiazem produced no alteration of ventricular repolarization suggests that electrophysiologic properties other than calcium channel blockade, presumably blockade of potassium channels,[17] are responsible for the effects of bepridil on repolarization. Bepridil-induced prolongation of QT interval was not due to a decrease in heart rate since QTc interval (i.e., QT interval normalized for heart rate) was also prolonged. Moreover, bepridil had no significant effect on heart rate in this study (Figure 1).

On average, the effects of bepridil therapy on ventricular repolarization reached a steady state within 2 weeks (Figure 1, Table II). These results, however, do not indicate that an electrocardiogram recorded 14 days after initiation of a treatment with bepridil is always sufficient to assess its effects on QT or QTc intervals in a given patient. Indeed, among the 30 patients with <40 ms QTc prolongation on day 14 compared with baseline, 13 (43%) exceeded this limit on at least 1 of the following visits. Moreover, among the 11 patients treated with bepridil in whom QTc interval reached a value of 500 ms, this limit was attained only once on day 14. Assuming a mean (± standard deviation) half-life of approximately 42 ± 12 hours for bepridil,[18] 2 weeks should have been a sufficient time for bepridil effects to reach a steady state in the vast majority of patients. This discrepancy suggests that pharmacokinetic characteristics are not the sole determinant of the time-course of bepridil-induced QT prolongation.

Bepridil did not alter the ability of QT interval to shorten with increased heart rate. Compared to diltiazem, it produced an upward shift of the change in QT interval versus change in RR interval relation relative to baseline and these effects of bepridil on QT interval were seen in the whole range of heart rate changes observed in our patients (Figure 2). Baseline QTc interval was a statistically significant predictor of the absolute change in QTc interval duration produced by bepridil (Figure 3). QTc prolongation with bepridil tended to be more pronounced in patients with a relatively short baseline QTc interval. However, QTc interval decreased during bepridil therapy in some patients with long initial QTc intervals (Figure 3). Moreover, QT interval remained within normal limits (≤480 ms) in this study. It must be emphasized that, in our study, baseline QTc interval was significantly longer in the 11 patients in whom QTc interval once reached a value of ≥500 ms during bepridil compared to the 34 patients in whom this limit was never reached. Nevertheless, the absolute change in QTc interval duration from baseline was greater in patients with a relatively short initial QTc interval (Figure 3). Thus, our results suggest that a short baseline QTc interval should not be viewed as a protective factor against bepridil-induced QTc prolongation.

Bepridil produced more QTc interval prolongation in patients with a slow heart rate at baseline than in those with a comparatively rapid heart rate (Figure 4). In a study performed in normal volunteers, it was also found that the effects of bepridil on ventricular repolarization increase when heart rate decreases.[19] This rate-dependence of class III activity is consistent with several in vitro results that showed that the effects of several QT-prolonging drugs on action potential duration increase with a decreased pacing rate.[20-23] It has been suggested that this phenomenon might be due to inhibition of a time-dependent outward current. The fact that bepridil-induced prolongation of ventricular repolarization is more pronounced in patients with slow heart rate may indicate that bradycardia before administration of a drug with class III activity increases the risk of excessive QT prolongation and hence the risk of torsades de pointes. In fact, among 9 patients with bepridil-induced torsades de pointes,[10] 2 had no hypokalemia and did not receive concomitant diuretic therapy. These 2 patients had the slowest heart rate both during treatment with bepridil and after discontinuation of bepridil therapy.

In our study, only 11 patients (24%) had QTc interval prolongation of ≥500 ms during bepridil therapy. Thus, in more than 3 of 4 patients, bepridil did not pro-

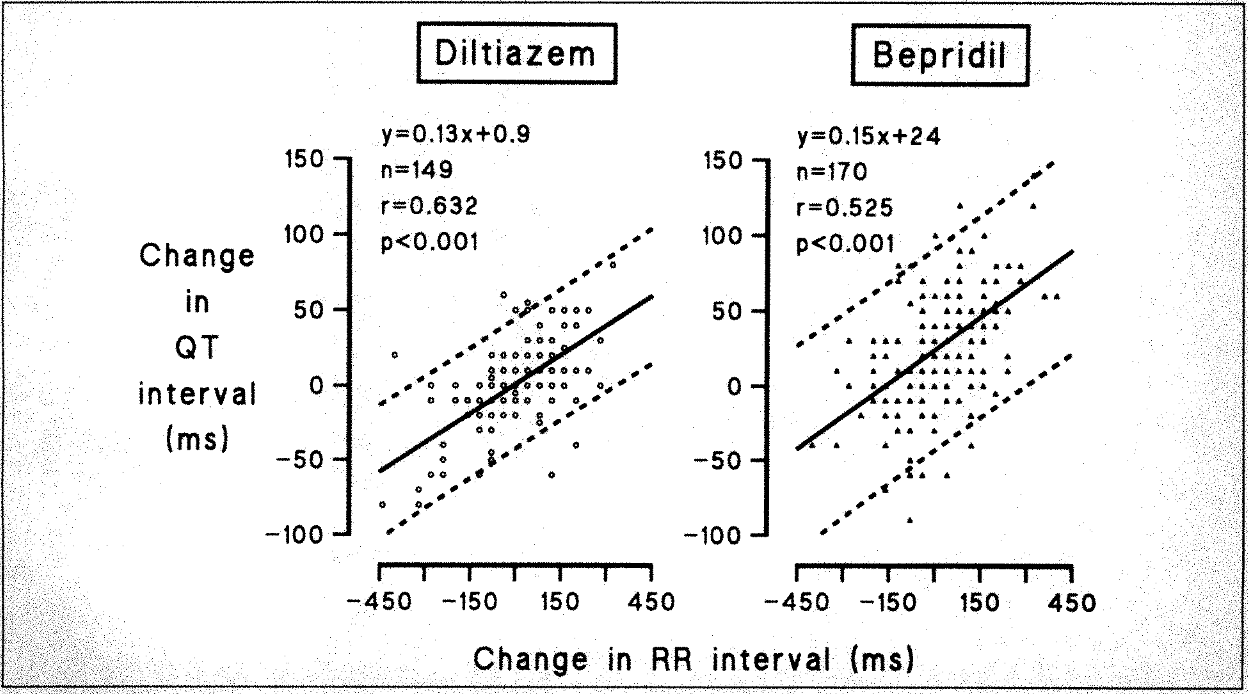

FIGURE 2. Relation between the absolute change in QT interval from baseline and the absolute change in RR interval from baseline on all follow-up visits with bepridil and with diltiazem. The predicted 95% confidence intervals are represented. The intercept of the regression curve was significantly higher during bepridil therapy than during diltiazem therapy.

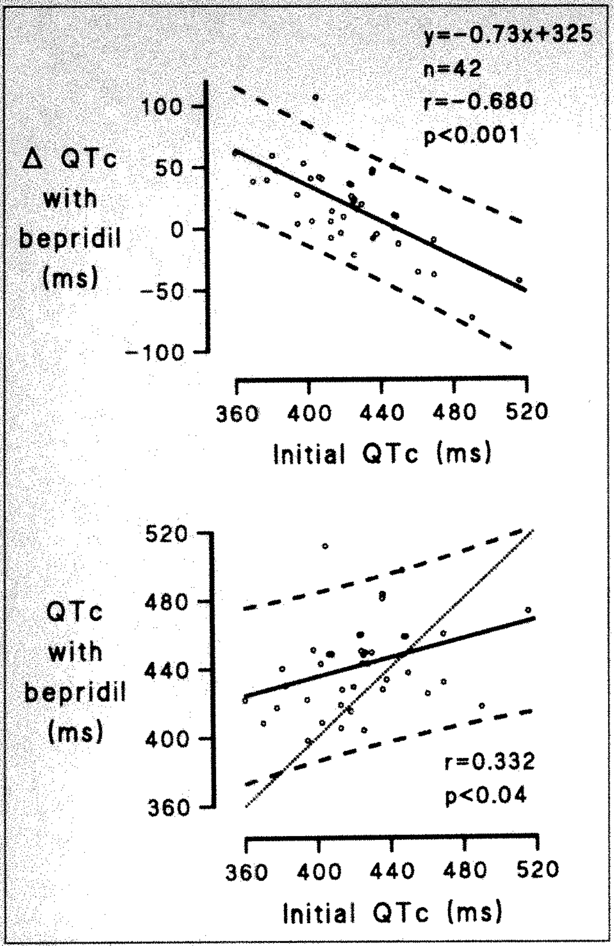

FIGURE 3. Relation between the absolute change in QTc interval on day 14 and its pretreatment value. *Top,* absolute change in QTc interval from baseline on day 14 as a function of pretreatment QTc interval. *Bottom,* plot of QTc interval on day 14 as a function of baseline QTc interval. The *dotted line* represents the line of identity. The predicted 95% confidence intervals are represented.

duce marked effects on ventricular repolarization. In addition, despite prolonged QTc interval duration in 11 subjects, no torsades de pointes or other proarrhythmia occurred in any patient. Also, no proarrhythmia occurred in any of the 116 patients who were randomized to bepridil therapy in the main study. Exclusion of patients with a history of ventricular arrhythmia and with any factor known to promote torsades de pointes may have contributed to the latter favorable finding. Also, owing to the low incidence of torsades de pointes, our study lacked power to detect bepridil-induced proarrhythmia. There is still a great deal of controversy on whether QT prolongation is antiarrhythmic or proarrhythmic.[24,25] Dispersion of refractoriness (and QT interval duration) increases with decreased heart rate and may contribute to the generation of ventricular arrhythmias.[26,27] As discussed by Roden and Woosley,[24] the absolute duration of QT interval gives no indication of the range of repolarization times or refractory periods in individual areas within the myocardium. Thus, there is no clear evidence that QT interval prolongation is associated with dispersion of ventricular repolarization. Therefore, drug-induced QT interval prolongation in itself may not be a predictor of proarrhythmia (or of antiarrhythmic efficacy).[25,28] In fact, in a recent double-blind, placebo-controlled study, the QT-prolonging serotonin antagonist ketanserin did not produce proarrhythmic effects despite significant QT prolongation in at least 30% of patients.[29] Our study supports the view that QT interval prolongation is not harmful per se.

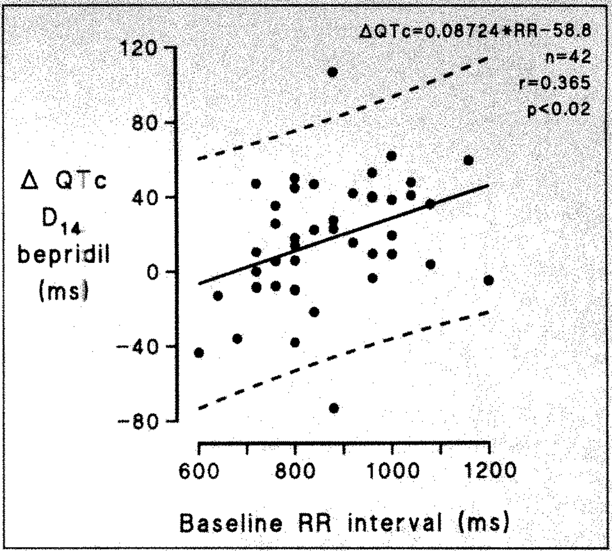

FIGURE 4. Relation between the change in absolute QTc interval on day 14 and the corresponding pretreatment RR interval. The predicted 95% confidence intervals are represented.

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APPENDIX

The following investigators were involved in the Multicenter Bepridil-Diltiazem Study: Aleonard J, MD, *Margaux*; Ben Naceur M, MD, *Tunis, Tunisia*; Bernasconi P, MD, *Amiens*; Bevernage F, MD, *Lescar*; Bouye N, MD, Christophe H, MD, *Bourg sur Gironde*; Chemin P, MD, *Le Bouscat;* Claroux P, MD, Dartenuc J, MD, Ribleur A, MD, *Bruges*; Colcher E, MD, *Montereau*; Delprat J, MD, *Bergerac*; Dodemant P, MD, Masson J, MD, *Tours*; Droniou J, MD, Jullien J, MD, *Paris;* Farrat N, MD, *Blaye*; Fourdilis L, MD, *Paimpol*; Frances Y, MD, *Marseille*; Friocourt P, MD, *Saint-Aignan*; Gillet B, MD, *Podensac*; Giraud M, MD, *Montreuil*; Granatelli D, MD, *Brest*; Granier J, MD, *Pontoise*; Jarnage J, MD, *Saint-André-de-Cubzac;* Lafitte G, MD, *Pontivy*; Larrieu J, MD, *Langoiran*; Le Leyour N, MD, *Bordeaux*; Marco J, MD, *Toulouse*; Moisson P, MD, *Port Marly*; Mothes P, MD, *Pau*; Neveux E, MD, *Sèvres;* Noury J, MD, *Provins*; Olive T, MD, *Gap*; Pauchant M, MD, *Wattrelos*; Pujos N, MD, *Lussac*; Roy M, MD, *Cahors*; Wind P, MD, *Marmande.*

Effects of Intravenous Verapamil on Left Ventricular Relaxation and Filling in Stable Angina Pectoris

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Left ventricular (LV) diastolic function is often impaired in coronary artery disease (CAD). To assess whether verapamil could improve LV diastolic properties, 12 patients with CAD undergoing right- and left-sided cardiac catheterization, as well as simultaneous radionuclide angiography, were studied before and during intravenous administration of verapamil (0.1 mg/kg as a bolus followed by 0.007 mg/kg/min). The heart rate was kept constant by atrial pacing in both studies. LV pressure-volume relations were obtained. Verapamil decreased LV systolic pressure (130 ± 22 to 117 ± 16 mm Hg, $p < 0.01$) and the end-systolic pressure/volume ratio (2.4 ± 1.3 to 1.6 ± 0.5 mm Hg/ml, $p < 0.05$), and increased LV end-diastolic (13 ± 4 to 16 ± 4 mm Hg, $p < 0.02$) and pulmonary capillary pressures (10 ± 5 to 12 ± 5 mm Hg, $p < 0.005$). Despite such negative inotropic effects, cardiac index increased (3.4 ± 0.7 to 3.9 ± 0.6 liters/min/m^2, $p < 0.02$). The time constant of isovolumic relaxation shortened (63 ± 14 to 47 ± 9 ms, $p < 0.02$); peak filling rate increased (370 ± 155 to 519 ± 184 ml/s, $p < 0.001$; 2.6 ± 1.1 to 3.3 ± 0.9 end-diastolic counts/s, $p < 0.02$; and 4.1 ± 1.6 to 5.5 ± 1.5 stroke counts/s, $p < 0.001$). Percentage changes in peak filling rate were related to percentage changes in the time constant of isovolumic relaxation, the pressure asymptote, pulmonary capillary pressure, end-diastolic volume, and an index of LV diastolic asynchrony ($r = 0.930$, $R^2 = 0.864$, $F = 7.636$, $p = 0.014$). Late diastolic filling was not affected by verapamil. Thus, intravenous verapamil administration in patients with CAD improved LV isovolumic relaxation and early filling. These effects are likely the consequence of both the drug's direct action on myocardium and changes in the loading conditions.

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Ischemia is capable of impairing the normal pattern of left ventricular (LV) diastolic function, as it slows relaxation[1-3] and reduces early filling.[3-6] In patients with coronary artery disease (CAD), LV peak filling rate, a clinically useful estimate of LV filling properties, is diminished even at rest and in the absence of altered systolic performance.[5,7-9] Because diastolic dysfunction is apt to induce symptoms of congestive heart failure even when systolic function is preserved,[10,11] it would be important to assess whether this diastolic dysfunction could be pharmacologically reverted.

Verapamil has been shown to improve LV relaxation and filling in hypertrophic cardiomyopathy[12,13] and hypertension.[14,15] In patients with CAD similar effects have been observed in noninvasive studies.[16,17] However, changes in loading conditions associated with the drug could have affected those results to some extent: in fact, an increase in peak filling rate after verapamil administration is not exclusively related to improved diastolic function, but could also be the consequence of heightened filling pressures. The present investigation analyzes the effects of acutely administered verapamil on LV relaxation and filling in patients with CAD, in an invasive study where changes in load could be accounted for by using analysis of pressure-volume relation.

METHODS

Patient selection: We studied 12 patients undergoing diagnostic cardiac catheterization and coronary angiography. They were enrolled according to 4 criteria: (1) no previous myocardial infarction; (2) no associated cardiac or pulmonary diseases, hypertension, diabetes mellitus or history of alcohol abuse; (3) stable angina pectoris with mild-to-moderate symptoms, enabling discontinuation of therapy; and (4) normal LV global and regional performance. There were 11 men and 1 woman, ranging in age from 42 to 57 years (mean 49). All gave informed consent for participation in the study, which had been approved by the "ad hoc" institutional committee.

Study protocol: Drugs were withdrawn at least 5 half-lives before the study; however, short-acting nitrates were allowed when necessary.

All patients underwent simultaneous right- and left-sided cardiac catheterization and radionuclide angiography. Because it was expected that intravenous verapamil would induce a decrease in blood pressure and

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hence a reflex increase in heart rate, a baseline study was obtained during atrial pacing at a heart rate approximately 15 beats above the spontaneous sinus rhythm. At the end, the pacemaker was turned off and verapamil was administered intravenously as a bolus of 0.1 mg/kg over 3 minutes, followed by an infusion of 0.007 mg/kg/min throughout the study; 10 minutes after the end of the bolus administration, atrial pacing was resumed at the same rate as before and the second study was begun.

Cardiac catheterization and hemodynamic measurements: A 7Fr Swan-Ganz thermodilution catheter (Edwards Laboratories) was introduced into the pulmonary artery, to measure cardiac output and pulmonary "wedge" pressure. A 7Fr or 8Fr pig-tail high fidelity transducer-tipped catheter (Honeywell) was also advanced into the left ventricle, for measurement of LV pressure and cineventriculography. LV pressure and its first derivative (dP/dt) were recorded at a paper speed of 250 mm/s, and LV pressure was also sent to the gamma camera-computer system for building pressure-volume curves. High-speed LV pressure and dP/dt waves were digitized at 4-ms intervals for calculation of the time constant of isovolumic relaxation using the variable asymptote model.[18] Briefly, dP/dt values were plotted as a function of the corresponding pressure values, starting from minimum dP/dt and ending when pressure was 1/e of its initial value. The time constant of isovolumic relaxation was computed as the negative

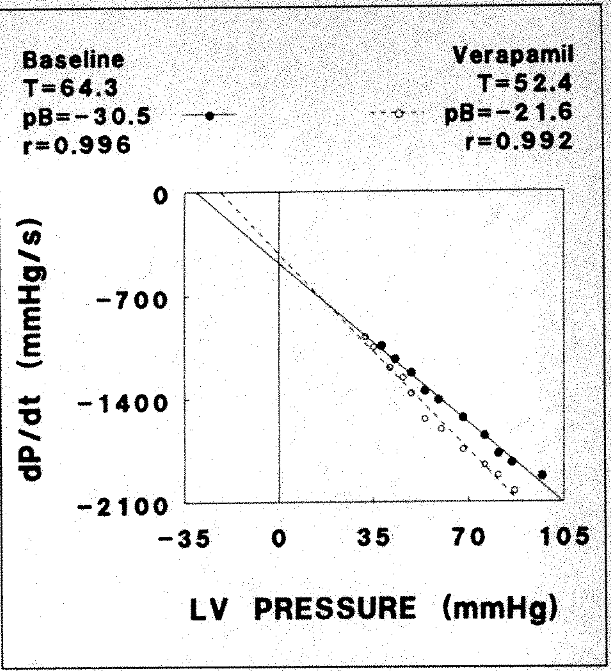

FIGURE 1. Negative limb of the first derivative of left ventricular pressure plotted as a function of pressure at baseline *(closed symbols, solid line)* and during verapamil administration *(open symbols, dashed line)* in a patient. There is a steeper slope and increased pressure asymptote during verapamil. dP/dt = first derivative of the time-pressure curve; LV = left ventricular; pB = pressure asymptote; r = correlation coefficient; T = time constant of isovolumic relaxation.

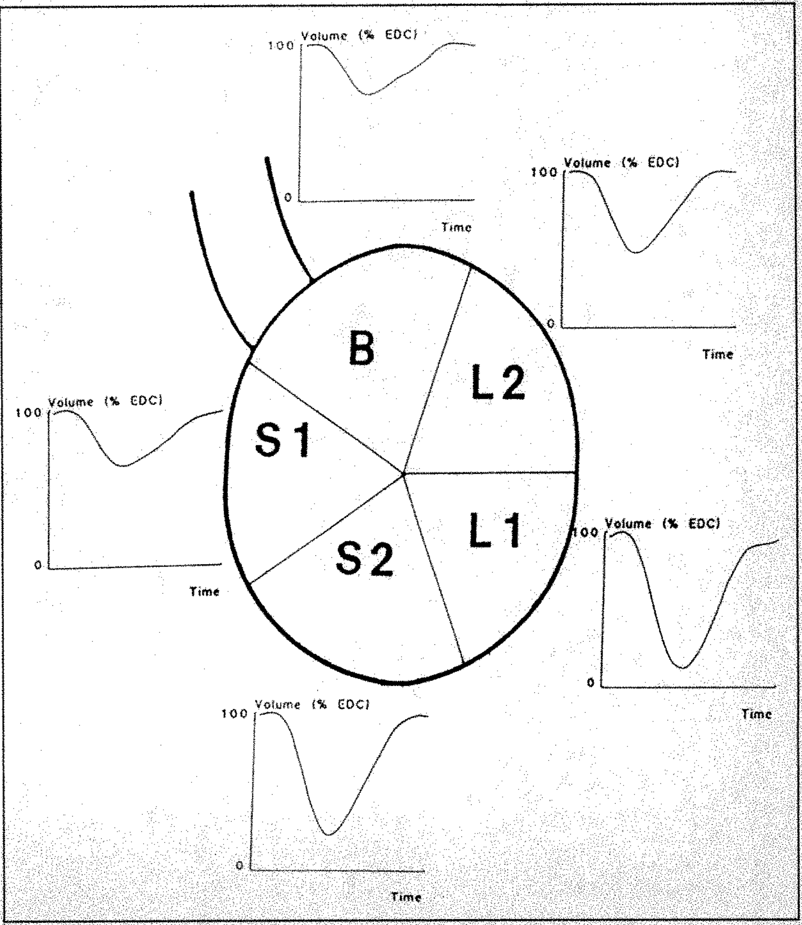

FIGURE 2. Schematic representation of a left ventricular region of interest divided into 5 sectors. A time-activity curve from each sector is also displayed. Data pertaining to *sector B*, which includes the area of mitral and aortic valves, were not used in the analysis. EDC = end-diastolic counts.

TABLE I Hemodynamics and Indexes of Systolic Performance Before and During Verapamil Administration

	Baseline	Verapamil	p Value
Heart rate (beats/min)	95 ± 10	95 ± 10	NS
Left ventricular pressure (mm Hg)			
Systolic	130 ± 22	117 ± 16	0.01
End-diastolic	13 ± 4	16 ± 4	0.02
Pulmonary wedge pressure (mm Hg)	10 ± 5	12 ± 5	0.005
Cardiac index (liters/min/m²)	3.4 ± 0.7	3.9 ± 0.6	0.02
End-diastolic volume (ml)	145 ± 29	157 ± 24	NS
Ejection fraction (%)	63 ± 9	60 ± 12	NS
End-systolic pressure/volume (mm Hg/ml)	2.4 ± 1.3	1.6 ± 0.5	0.05
TPER coefficient of variation (%)	10 ± 7	12 ± 7	NS

NS = not significant; TPER = time to peak ejection rate.

reciprocal of the slope of this linear relation, whereas the asymptote was calculated as the extrapolated pressure value at which dP/dt reached 0 (Figure 1). Completeness of relaxation was assessed by the number of time constants elapsed from minimum dP/dt to the lowest LV pressure.[2]

Cineventriculography was performed immediately after the end of the experimental protocol, during atrial pacing and verapamil infusion, in the 30° right anterior oblique view. The first well-opacified sinus beat not following an ectopic beat was analyzed for end-diastolic volume,[19] using a graphic tablet interfaced with a computer (Digital PDP 11/34).

Radionuclide angiography: Equilibrium radionuclide angiography was performed with the patients lying in the supine position on the cardiac catheterization cradle. Red blood cells were labeled in vivo with 20 to 25 mCi of technetium 99-m and counts were collected by a small field-of-view Anger camera (Siemens LEM ZLC), oriented in a 45° left anterior oblique view, with a 15° caudal tilt. Images were acquired with a 2× digital zoom, in frame mode, at a framing rate of 50 frames/s (i.e., 20 ms/frame) with a gate tolerance of ±5%. At least 150,000 counts/frame were collected in the baseline study, whereas the verapamil study was acquired for the same time as the baseline study, in order for the 2 studies to consist of the same number of cardiac cycles (as heart rate was kept constant).

The time-activity curve recorded in the verapamil study was expressed in ml by normalizing its end-diastolic number of counts to end-diastolic volume measured by contrast angiography. The baseline time-activity curve was then normalized to the verapamil curve, after correction for the isotope decay.

Ejection fraction was calculated on the "raw" time-activity curve, whereas peak filling rate was computed, after filtering using a Fourier expansion with 5 harmonics, as the maximum of its first derivative and expressed in ml/s or normalized by end-diastolic as well as stroke number of counts; time to peak filling rate was measured from the R wave. Further details on radionuclide angiography methods, accuracy and reproducibility of these measurements in our laboratory have been previously reported.[14]

LV regional analysis was performed using a computer algorithm that identified the center of gravity of the LV region of interest and divided it into 5 sectors of equal angle starting at 3 o'clock and proceeding counterclockwise. The region that includes the mitral and aortic valves (Figure 2) was not used in the analysis. Time-activity curves were filtered, after background subtraction, using a Fourier expansion with 3 harmonics. Peak ejection rate (as the minimum of the first derivative of the time-activity curve) and peak filling rate were measured in each of the 4 sectors. We evaluated

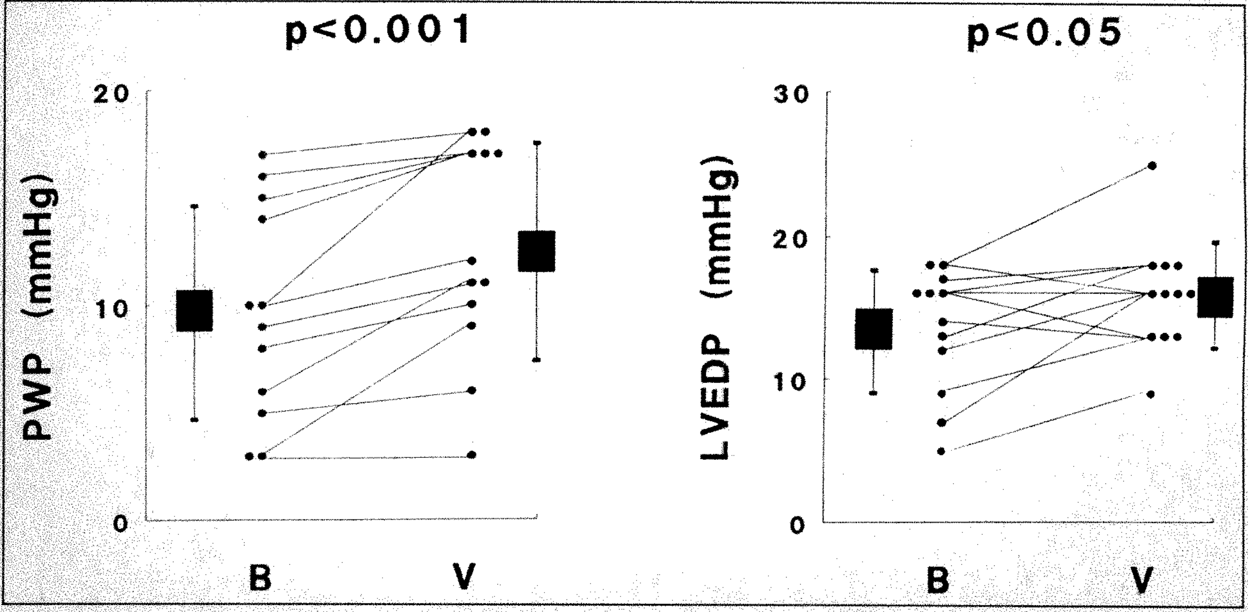

FIGURE 3. Individual changes induced by verapamil on pulmonary wedge pressure (PWP) *(left)* and left ventricular end-diastolic pressure (LVEDP) *(right)*. B = baseline; V = verapamil.

TABLE II Diastolic Function Before and During Verapamil Administration

	Baseline	Verapamil	p Value
T (ms)	63 ± 14	47 ± 9	0.02
Pressure asymptote (mm Hg)	−22 ± 22	−4 ± 9	0.05
Ts elapsed from minimum dP/dt to lowest pressure	1.9 ± 0.3	2.3 ± 0.3	0.02
Peak filling rate			
ml/s	370 ± 155	519 ± 184	0.001
End-diastolic counts/s	2.6 ± 1.1	3.3 ± 0.9	0.02
Stroke counts/s	4.1 ± 1.6	5.5 ± 1.5	0.001
TPFR (ms)	467 ± 61	467 ± 43	NS
TPFR coefficient of variation (%)	11 ± 5	7 ± 7	NS
k (mm Hg/ml)	0.022 ± 0.015	0.019 ± 0.012	NS

k = constant of chamber stiffness; NS = not significant; T = time constant of isovolumic relaxation; TPFR = time to peak filling rate.

LV systolic and diastolic asynchrony by measuring the coefficient of variation of the 4 regional values of time to peak ejection and filling rates, respectively.

Left ventricular pressure-volume analysis: LV pressure was sent to a custom-designed interface (Medie) connected to the gamma camera-computer system (Digital PDP 11/34). This interface wrote the pressure values into the scintigraphic matrixes: in this way LV pressure curves have the same gating point and framing rate, and represent an average of the same cardiac cycles as the time-activity curves, with which they were combined to create high temporal resolution pressure-volume loops. Pressure curves obtained by this method are virtually noise-free and do not require filtering.

The LV constant of chamber stiffness (k) was measured on the part of pressure-volume loops from minimal pressure to end-diastole, according to the formula $P = Ae^{kV}$, where P is pressure, V is volume and A is a constant.

Statistical methods: Data are expressed as mean ± standard deviation. Paired *t* test and linear regression analysis were used when appropriate. Determinants of changes induced by verapamil were assessed by stepwise multiple regression analysis.[20]

RESULTS

Coronary arteriography findings: Significant (>75%) 1-vessel and 2-vessel narrowing was found in 4 patients each; 3 patients had 3-vessel CAD, whereas the remaining patient had 50% stenosis in 2 vessels.

Hemodynamics: LV systolic pressure decreased and both LV end-diastolic and pulmonary "wedge" pressure increased (Table I) (Figure 3). The end-systolic pressure-volume relation shifted downward and rightward in 7 patients, rightward and slightly upward in 3 and downward and leftward in 2. Hence, the end-systolic pressure-volume ratio decreased significantly. Despite this evidence for a negative inotropic effect, cardiac index increased (Table I).

Left ventricular diastolic function: The time-constant of isovolumic relaxation shortened in all but 3 patients (Figure 1), and significantly in the group; its pres-

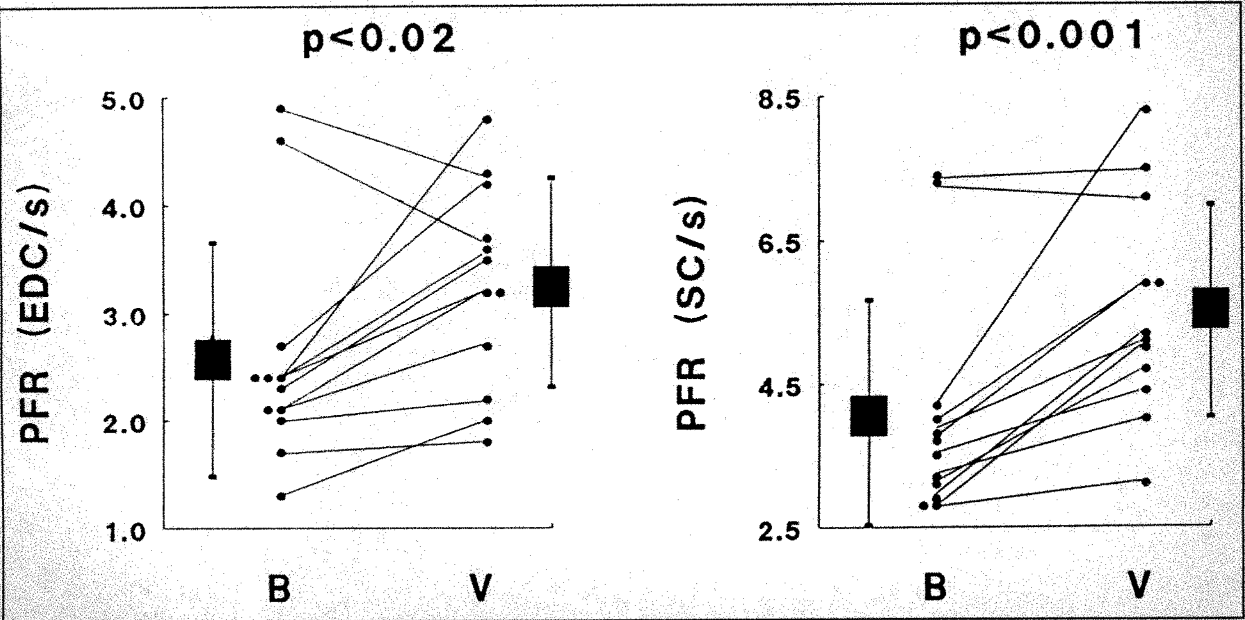

FIGURE 4. Individual changes induced by verapamil on peak filling rate (PFR) normalized to end-diastolic counts/s *(right)* and stroke counts (SC)/s *(left)*. Abbreviations as in Figures 2 and 3.

TABLE III Determinants of Percentage Changes in Peak Filling Rate (Stroke Counts/s)

Percentage Changes	Coefficient	Standardized Coefficient
T	0.649	0.782
Pressure asymptote	−0.092	−0.658
Pulmonary wedge pressure	−0.363	−0.641
End-diastolic volume	0.859	0.521
TPFR coefficient of variation	−0.199	−0.432
Multiple r = 0.930	multiple R^2 = 0.864	F = 7.636 p = 0.014

T = time constant of isovolumic relaxation; TPFR = time to peak filling rate.

sure asymptote increased and the number of time constants elapsed from minimum dP/dt to the lowest LV pressure increased (Table II).

Peak filling rate increased significantly when normalized to end-diastolic and stroke counts/s (Figure 4), as well as expressed in ml/s (Table II).

The coefficient of variation of time to peak filling rate exhibited a nonsignificant trend toward decrease ($p = 0.10$). Moreover, a linear relation was found between percentage changes in diastolic asynchrony and percentage changes in the time constant of isovolumic relaxation (Figure 5).

The diastolic part of the pressure-volume loops showed no modifications in LV compliance in 8 of the 12 patients (Figure 6), an improvement in 3 patients and worsening in 1. These results are consistent with the lack of significant changes observed in the constant of chamber stiffness.

Determinants of changes in peak filling rate: In the multiple regression analysis we used peak filling rate normalized to stroke counts, because peak filling rate in end-diastolic counts depends on ejection fraction.[5] The percentage changes in peak filling rate were tested against percentage changes in pulmonary wedge pressure, ejection fraction, end-systolic pressure/volume ratio, end-diastolic volume, indexes of systolic and diastolic asynchrony, the time constant of isovolumic relaxation and its pressure asymptote. Table III lists the results of the stepwise multiple regression analysis.

Effects in patients with minor afterload changes: We analyzed separately a subgroup of 5 patients in whom LV systolic pressure decreased ≤5% during verapamil administration. The effects of verapamil in this subgroup differed from those in the whole group in that there were no significant changes in LV systolic pressure (as expected), a significant decrease in ejection fraction (from 56 ± 7 to 50 ± 7%; $p < 0.05$) and an increase in end-diastolic volume (132 ± 12 to 155 ± 16 ml; $p < 0.005$). The increase in peak filling rate, normalized to stroke counts, almost reached the significance level (4.3 ± 1.8 to 6.1 ± 1.7; $p < 0.07$), whereas the time constant of isovolumic relaxation showed a nonsignificant trend toward improvement (62 ± 18 to 54 ± 17 ms).

DISCUSSION

Hemodynamic effects: Intravenous verapamil administration induced a systemic vasodilation, as shown by the significant decrease in LV systolic pressure and the concomitant increase in cardiac index (Table I). Ejection fraction showed a nonsignificant trend toward a decline: this finding is the consequence of 2 opposite effects, namely afterload reduction (which would increase ejection fraction) and the drug's negative inotropic effect (which would decrease it); in fact, in the subset of patients in whom LV systolic pressure decreased ≤5%, ejection fraction decreased significantly. This known negative inotropic property of verapamil[16,21,22] is also suggested by the significant decrease in the end-systolic pressure/volume ratio. LV end-diastolic and mean pulmonary wedge pressures increased slightly but significantly during verapamil administration (Table I and Figure 3), as a result of the reduced LV systolic performance.

Effects of verapamil on diastolic mechanics: A shortening in the time constant of isovolumic relaxation and an increase in the asymptote of LV pressure decay were observed (Table II and Figure 1). Moreover, the number of time constants of isovolumic relaxation elapsed from minimum dP/dt to the lowest pressure[2] was increased during verapamil (Table II), which indi-

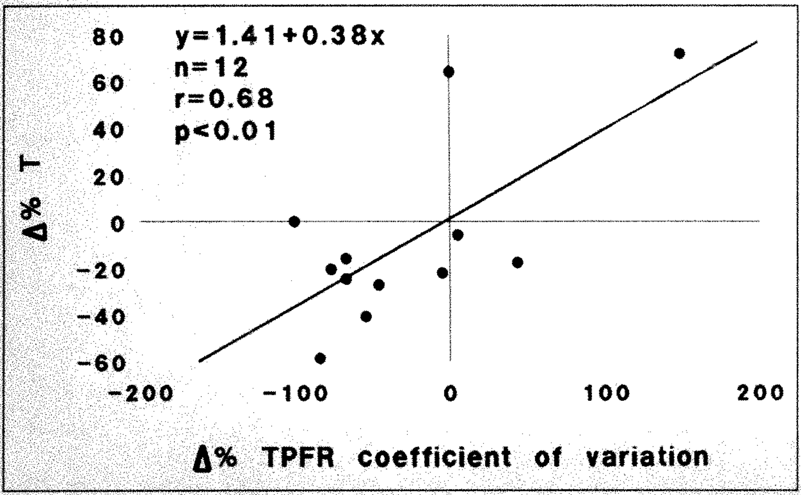

FIGURE 5. Verapamil-induced percentage changes in the time constant of isovolumic relaxation plotted as a function of percentage changes in the coefficient of variation of sector time to peak filling rate. T = time constant of isovolumic relaxation; TPFR = time to peak filling rate.

cates that the left ventricle, when reaching minimum pressure, was more fully relaxed. These concomitant changes indicate that verapamil administration improved the isovolumic relaxation by making it faster and more complete. Of note, the time constant of isovolumic relaxation was prolonged at baseline (i.e., >53.3 ms, the upper limit of the 99% confidence interval in a control group in whom this parameter was measured with the same method used herein[23]) in 8 of the 12 patients, and it shortened with verapamil in 7 of them.

Early filling was also influenced by verapamil administration, as peak filling rate increased (Table II and Figures 4 and 6). Such an increase is more evident when peak filling rate is expressed in ml/s or normalized to stroke counts: in fact, a trend toward an enlargement in end-diastolic volume and a reduction in ejection fraction were seen, which both tend to decrease peak filling rate in end-diastolic counts/s. Peak filling rate increased in only and all patients with subnormal basal values (i.e., <2.8 end-diastolic counts/s[14]); this finding is similar to that observed with verapamil in patients with secondary LV hypertrophy,[13,14] and, together with the shortening of the time constant of isovolumic relaxation in 7 of the 8 patients starting out with prolonged basal values, suggests that verapamil effects are more pronounced in patients with impaired diastolic function.

LV diastolic asynchrony showed only a trend toward reduction; its changes, however, played a role in influencing early diastolic function. In fact, we found a more marked improvement in isovolumic relaxation in those patients in whom verapamil led to a reduced asynchrony (Figure 5). Furthermore, stepwise multiple regression analysis showed that the effects of verapamil on peak filling rate were mediated through its action on isovolumic relaxation (as the time constant and the pressure asymptote were the most consequential determinants), on filling pressure and on diastolic asynchrony (Table III). Interestingly, another determinant was changes in end-diastolic volume: this finding suggests that verapamil acted on the rate and also on the extent of filling. This goes along with the increase in cardiac index despite the evidence for a negative inotropic effect.

In contrast to the beneficial effects on isovolumic relaxation and early filling, no improvement in compliance could be detected in most patients, either qualitatively or by the lack of changes in the constant of LV chamber stiffness.

Mechanisms by which verapamil influences early diastolic function: Verapamil could improve isovolumic relaxation and hence magnify peak filling rate through its direct effects on myocardium. Lorell and Barry[24] have demonstrated in isolated myocardial cells that high calcium concentration resulted in a decreased velocity of relaxation, and that such a phenomenon was abolished by verapamil, whereas, in the presence of low calcium concentration, verapamil slowed relaxation. Further evidence for different effects of verapamil on myocardium depending on its condition is provided by a

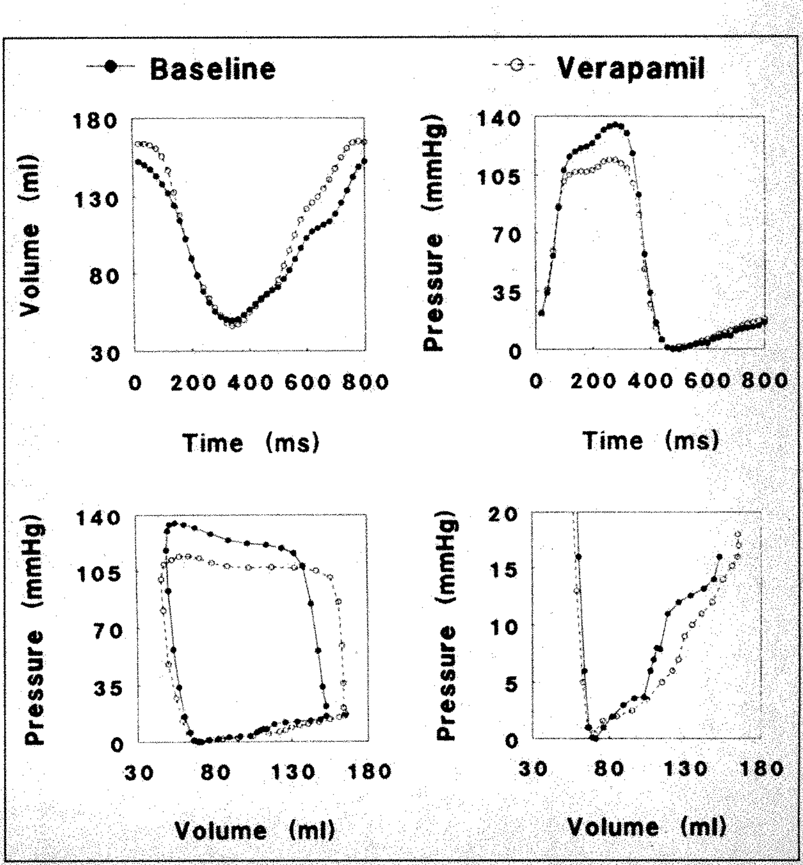

FIGURE 6. Left ventricular (LV) time-volume curves *(top left)*, time-pressure curves *(top right)* and pressure-volume curves *(bottom left)* in a patient before *(closed symbols, solid lines)* and during verapamil administration *(open symbols, dashed lines)*. *Bottom right*, a pressure-volume diagram at an expanded pressure scale shows further details of the diastolic pressure-volume relation. Verapamil administration induced an increased filling velocity in the time-volume curve, a decrease in LV systolic pressure and a modest increase in LV end-diastolic pressure; the pressure-volume relation shows an increased stroke volume as well as a downward shift of the end-systolic point, whereas the diastolic portion of the curve shows no changes.

study showing improved filling rate in only the ischemic regions of the left ventricle.[21] Because experimental ischemia is associated with increased myocardial calcium concentration,[25] one could conjecture that verapamil exerted beneficial effects on ischemic regions and that such effects would reduce asynchrony and enhance global diastolic function. This hypothesis is strengthened by the fact that most patients presented with abnormal isovolumic relaxation and early filling in the baseline and that verapamil proved beneficial in the vast majority of them (7 of 8 for isovolumic relaxation and 10 of 10 for peak filling rate).

In addition, we have shown that changes in diastolic asynchrony did contribute to variations in isovolumic relaxation (Figure 5) and peak filling rate (Table III). This suggests that the effect of verapamil on LV areas with some degree of chronic, nonclinical ischemia[26] was more conspicuous than in normal areas, and it was one of the mechanisms concurring to improved global diastolic function.

However, in the present study verapamil led to an elevation in preload (Figure 3) and a reduction in afterload. While a decrease in afterload is capable of improving relaxation,[27] a preload elevation results in an enhanced rate of filling[28]; thus, both these changes in loading conditions may have contributed to the improvement in early diastolic function. Walsh and O'Rourke[29] have documented in an elegant study that systemic administration of verapamil did not alter diastolic function in nonischemic dogs, and when associated with β blockers to prevent the adrenergic activation due to its peripheral effects, it worsened relaxation; analogously, intracoronary administration of verapamil only exerted a negative inotropic and consequently negative lusitropic action. To isolate the direct effects of verapamil from those mediated through changes in afterload, we considered separately 5 patients with minor afterload changes (as estimated by LV systolic pressure decrease $\leq 5\%$): they had a trend toward elevation in peak filling rate and improved isovolumic relaxation. This finding suggests that the improvement in isovolumic relaxation is not merely due to changes in afterload, but also to direct verapamil action on myocardium, whereas the increase in early filling depends on improvement in myocardial inactivation properties, increase in preload and reduction in asynchrony (Table III). Of interest, such an improvement in diastolic function occurred despite the evidence for a negative inotropic effect, which is known to delay relaxation.

Study limitations: A similar protocol should have been performed in a control group: if no changes were seen in normal subjects, that would mean that verapamil exerted its beneficial effects only on ischemic myocardium, not through changes in load. However, we considered it unethical to enroll normal subjects in an invasive protocol.

One of our enrollment criteria called for patients with normal LV wall motion: areas of LV scar and hence high degree of asynchrony[9] would have made the interpretation of verapamil effects on diastolic mechanics quite difficult. On the other hand, such patients had only moderate degree of diastolic impairment: it would be important, under a clinical point of view, that an improvement in early diastolic function be proved even in patients with severe, symptomatic diastolic dysfunction.

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Analysis of Programmed Stimulation Methods in the Evaluation of Ventricular Arrhythmias in Patients 20 Years Old and Younger

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The purpose of this study was to systematically evaluate programmed ventricular stimulation in patients <21 years of age undergoing electrophysiologic testing. A standardized protocol was applied in 55 consecutive patients (mean age 14 years) with the following clinical presentations: sustained ventricular tachycardia (VT) (n = 17); ventricular fibrillation (VF) (n = 7); syncope with heart disease (n = 10); nonsustained VT (n = 6); and syncope with an ostensibly normal heart (n = 15). The stimulation protocol consisted of 1 and 2 ventricular extrastimuli during sinus rhythm, followed by 1 to 4 (S_2, S_3, S_4, S_5) extrastimuli during pacing at 2 ventricular sites. Of the 17 patients with sustained VT, 12 had induction of the arrhythmia (sensitivity = 71%). Overall, 18 of 55 patients had inducible sustained VT, with this response significantly enhanced by use of S_4 or S_5 protocols ($p = 0.02$). Although no syncope patient with an ostensibly normal heart had inducible sustained VT, 7 had polymorphic nonsustained VT in response to ventricular stimulation. The mean number of extrastimuli preceding the induction of nonsustained or sustained VT or VF did not differ. The induction of VF in 5 cases during this study was preceded in each case by extrastimuli intervals ≤190 ms. Thus, data indicate that aggressive stimulation protocols appear to be required for induction of sustained VT in most young patients, nonsustained polymorphic VT as a response to aggressive programmed stimulation is of uncertain significance, and that coupling intervals ≤190 ms may correlate with the induction of VF.

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Despite the frequent use of programmed electrical stimulation for the evaluation of ventricular arrhythmias in young patients, systematic analysis of this testing has not been reported for this group. Programmed ventricular stimulation, initially devised for the evaluation of ventricular arrhythmias associated with myocardial infarction or ischemia[1-2] has subsequently been applied to diverse subgroups of patients.[3-7] Extensive analysis of the various protocols of programmed ventricular stimulation has been reported for adults [8-13] and has provided the basis for a more rational application of this testing and interpretation of results. In contrast, the sensitivity and specificity of programmed ventricular stimulation in young patients with ventricular arrhythmias are unknown. This study evaluates a defined stepwise protocol of programmed ventricular stimulation in young patients, both with and without clinically documented ventricular arrhythmias, to address the aforementioned uncertainties.

METHODS

Fifty-five consecutive patients, ages 0.2 to 20 years (mean 14 ± 4.5) undergoing electrophysiologic evaluation, provide the basis for this study. The indications for programmed stimulation were clinical sustained ventricular tachycardia (VT) (n = 17), resuscitation from ventricular fibrillation (VF) (n = 7), syncope, associated with palpitations and known cardiac disease (n = 10), nonsustained VT (n = 6) and syncope, with no recognized heart disease or tachyarrhythmia (n = 15). All patients with VT or VF had ≥1 lead of electrocardiographic documentation of their arrhythmia.

Of the 55 patients with documented or clinically suspect ventricular arrhythmias, 31 had recognized cardiovascular disease. Fifteen patients had prior surgical treatment of cyanotic congenital heart disease: tetralogy of Fallot (n = 9), transposition of the great arteries (n = 5), and total anomalous pulmonary venous return (n = 1). Three patients had congenital aortic stenosis, each with ≥1 prior surgical procedure. Three other patients had abnormalities of myocardial perfusion, due to an anomalous origin of the left coronary artery from the pulmonary artery in 1, and coronary arterial stenosis after Kawasaki disease in 2. Five patients had an idiopathic dilated cardiomyopathy, 3 the long QT syndrome, and 2 Wolff-Parkinson-White syndrome.

Ventricular function was evaluated in all patients by at least 1 method: echocardiography, radionuclide ventriculography, or cineangiography, prior to programmed

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ventricular stimulation. Noninvasive rhythm assessment included ≥ two 24-hour Holter recordings or observation on telemetry ≥48 hours in all patients.

Programmed ventricular stimulation protocol: Electrophysiologic studies were performed using sedation with chloral hydrate or diazepam as necessary, after informed consent had been obtained. All antiarrhythmic agents had been discontinued for a minimum of 5 drug half-lives before study. Three multiple electrode catheters were introduced percutaneously, and positioned under fluoroscopic control at the high right atrium, across the septal leaflet of the tricuspid valve to record the His bundle potential and at the apex of the right or left ventricle, based on the anatomy of the specific patient. A fourth catheter was positioned in the coronary sinus in 32 of 55 patients in this study. Intracardiac recordings were filtered below 30 and above 500 Hz and displayed simultaneously with 3 electrocardiographic leads. Before the initiation of programmed stimulation, R-2 defibrillator pads were applied to the anterior and posterior thorax of each patient and adapted to an external cardioverter-defibrillator. Programmed stimulation was performed with constant current pulses of 2 ms duration, delivered at twice diastolic threshold.

An initial determination of resting intracardiac intervals was followed by incremental atrial pacing for 30 seconds until 2:1 atrioventricular block occurred. Single and double atrial extrastimuli were next delivered at progressive 10-ms decrements until the atrial effective refractory period was attained.

Ventricular stimulation began with a single extrastimulus (S_2) delivered in late diastole during sinus rhythm, with progressively shorter 10 ms coupling intervals until the ventricular muscle effective refractory period was attained. S_2 was coupled 50 ms beyond the refractory period and a second extrastimulus (S_3) was introduced 350 ms later. S_3 was scanned through diastole by 10 ms decrements, until refractory, at which time S_2 and S_3 were moved in by 10 ms until S_2 was refractory. Single, double, triple (S_4) and quadruple (S_5) extrastimuli were next coupled to an 8-beat drive train of ventricular pacing at 600 or 500 ms at the ventricular apex using the same method. If no sustained ventricular arrhythmia was induced, the sequence of S_2-S_5 was repeated, coupled to a drive cycle of 400 ms.

The sequence of S_2 to S_5 coupled to 2 drive cycle lengths was repeated during pacing at the outflow tract, if no sustained ventricular arrhythmia was inducible at the apex. Additionally, in patients with documented sustained VT or VF with no inducible sustained arrhythmia, the S_2 to S_5 sequence was repeated during isoproterenol infusion (0.1 to 0.3 mcg/kg/min) after an increase in the basal heart rate by ≥25%. The baseline electrophysiology study was repeated in patients with inducible sustained VT or VF before electropharmacologic testing and those with clinically documented VT or VF, but no inducible sustained tachyarrhythmia.

Definitions: Sustained VT—Spontaneous VT ≥10 consecutive QRS complexes. Nonsustained VT—Spontaneous VT of 3–9 consecutive QRS complexes.[14] Inducible sustained VT—Initiation of VT ≥30 seconds duration or requiring termination due to hemodynamic compromise.[15] Inducible nonsustained VT—Initiation of self-terminating VT ≥6 beats and <30 seconds. Monomorphic VT—VT with a constant QRS morphology in ≥1 electrocardiographic lead.

Statistical analysis: Results are expressed as mean ± SD. Continuous variables were compared between groups by analysis of variance, with significant differences defined by Newman-Keul analysis. If only 2 groups were compared, Student's *t* test was used. Discrete variables were analyzed by chi-square or Fisher's exact test. Statistical significance was inferred at $p < 0.05$.

RESULTS

Induction of sustained ventricular tachycardia—correlation with type of heart disease and presenting arrhythmia: Overall, 18 of 55 patients (33%) studied by this protocol had induction of sustained VT. The rates of induction among patient subgroups are shown in Figure 1. Sustained VT was induced in 10 of 19 patients with congenital heart disease (53%), 4 of 12 with cardiomyopathy or primary electrical disease (33%) and 4 of 24 (16%) with no structural heart disease. The differences observed in the frequency of VT induction among

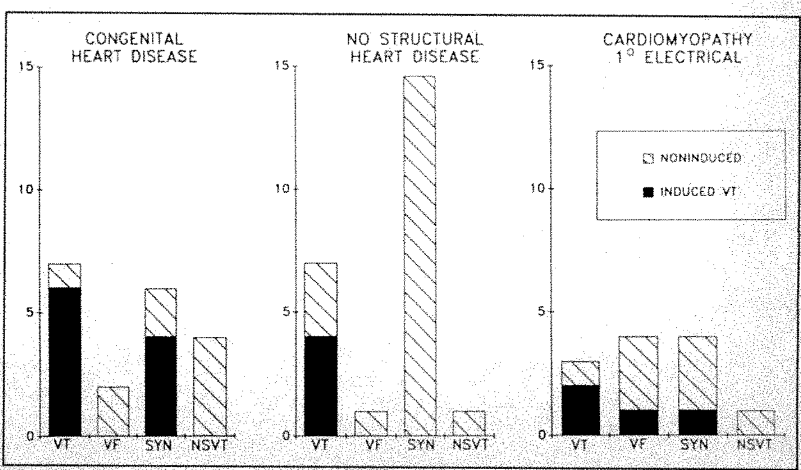

FIGURE 1. Induction of sustained ventricular tachycardia (VT) plotted as a function of the type of heart disease and presenting arrhythmia. Clinically documented VT was the only factor predictive of induction of sustained VT by programmed stimulation (p <0.01). NSVT = nonsustained ventricular tachycardia; SYN = syncope; VF = ventricular fibrillation.

TABLE I Correlates of Inducibility

Highest Grade Ventricular Arrhythmia	n	Mean No. of Extrastimuli	Mean Coupling Interval (ms)
RVR (1 to 5 beats)	8	2.2 ± 0.7*	269 ± 49
Nonsustained VT	17	2.7 ± 0.6	234 ± 23
Sustained VT	18	3.0 ± 0.6	237 ± 32
Ventricular fibrillation	5	3.2 ± 0.5	180 ± 12*

* p <0.01

Mean coupling interval = the interval between the last 2 extrastimuli; RVR = repetitive ventricular response; VT = ventricular tachycardia.

subgroups were not statistically significant, although patients with structural heart disease were more likely to have induction of VT. Ventricular function was subnormal in 8 of the 18 patients with inducible VT and 10 of 37 patients in whom VT was not inducible.

Analysis was next performed to determine whether significant differences in the frequency of VT induction occurred for each clinical arrhythmia among the various subgroups of cardiovascular disease. Although sustained VT was inducible in only 33% of patients in this series, 12 of 17 patients with clinical documentation of VT had induction (sensitivity = 71%). No patient with syncope and an otherwise normal cardiovascular evaluation had induction of sustained VT. VT was also induced in 5 patients with syncope and heart disease and in 1 patient resuscitated from VF. However, as VT had not been clinically documented in these patients, this data is not included in analysis of sensitivity. By univariate analysis, clinical documentation of VT was the only factor predictive of inducibility (p = 0.005).

Programmed stimulation techniques and the induction of ventricular tachycardia: The highest grade of inducible ventricular arrhythmia in each patient during the standardized pacing protocol was next evaluated. One patient had induction of VT during atrial and ventricular pacing, but only data for programmed ventricular stimulation are included in analysis. No patient had induction of sustained VT with S_2 or S_2, S_3 during sinus rhythm. During ventricular pacing, no patient had induction of VT with S_2 only and 3 patients had induction with S_2, S_3. In comparison, the use of S_2, S_3, S_4 or S_2, S_3, S_4, S_5 resulted in VT induction in 15 patients, a significantly (p <0.02) higher rate of inducibility (Figure 2). No correlation between the rate of VT and number of extrastimuli required for induction was observed.

Three patients with congenitial heart disease had induction of sustained VT only during pacing at the outflow tract, and 3 other patients were inducible only during isoproterenol infusion. Induction of sustained VT occurred with a drive cycle length of 600 or 500 ms in 15 of 18 patients. Use of the second drive cycle length of 400 ms was not systematically evaluated, as induction of sustained VT was the defined end point of testing. The mean number of extrastimuli resulting in the highest grades of inducible ventricular arrhythmia did not differ significantly (Table I).

Induction of ventricular fibrillation: Five patients had induction of VF as a response to programmed stimulation. Two had been resuscitated from prior sudden cardiac arrest and 3 had syncope in association with either the long QT syndrome or Wolff-Parkinson-White syndrome. The induction of VF occurred with a drive cycle length of 400 ms in 4 patients and S_3 to S_4 or S_4 to S_5 coupling intervals ≤190 ms in each patient (Figure 3). The coupling intervals preceding induction of VF were significantly shorter than those preceding other ventricular responses (Table I).

End points of programmed ventricular stimulation: Responses to programmed stimulation were reevaluated, with any response ≥6 beats of nonsustained VT or VF defined as significant. Overall, 40 of 55 patients (73%) had a positive response by this criterion, including 15 of 17 with clinical VT. However, 7 of 15 syncope patients without cardiovascular disease or clinical arrhythmia also tested positive by this criteria (Figure 4).

Morphology and reproducibility: The QRS morphology of inducible sustained VT was left bundle (n = 10), right bundle (n = 3), and indeterminate (n = 5)

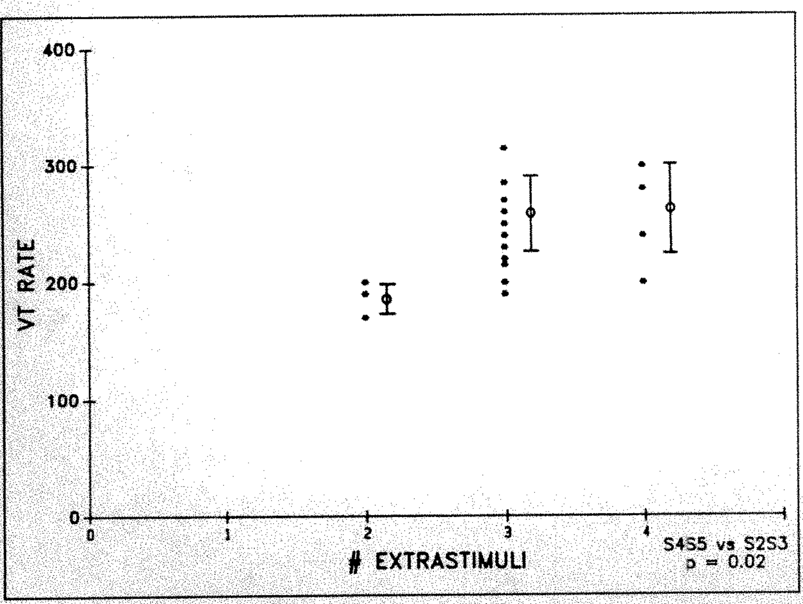

FIGURE 2. Number of extrastimuli required for induction of sustained ventricular tachycardia (VT). The use of 3 or 4 extrastimuli significantly enhanced the inducibility of sustained ventricular tachycardia (p = 0.02). No statistically significant correlation was observed between the number of extrastimuli and rate of inducible VT.

and concordant with the clinical VT in the 12 cases in which comparison was possible. The induction of sustained VT was reproducible in 14 of 18 patients at the second baseline test or during serial drug testing.

DISCUSSION

In contrast to most adults, an ischemic substrate of VT is infrequent in young patients.[16] Thus, interpretation of the responses to programmed ventricular stimulation in young patients, tested in accordance with adult protocols, must be questioned. In addition, differing stimulation techniques are frequently utilized during electrophysiologic testing.[17] This study was performed to systematically evaluate the responses to a standardized protocol of programmed ventricular stimulation in young patients.

Analysis of stimulation techniques: S_4 or S_5 stimulation sequences were required for the induction of sustained VT in 15 of 18 patients in this study. The minimal sensitivity of S_2 or S_3 protocols in young patients contrasts with studies of adults with coronary artery disease, in whom S_2 or S_3 protocols result in a 70–90% induction rate of VT.[12,18,19] The reported induction rates of VT in adults with nonischemic substrates of VT have been lower, comparable to the results in this series.[3,6]

The mechanism(s) of VT in young patients may differ, based, in part, on the presence or type of associated heart disease.[20–22] In addition, differing stimulation protocols and responses to stimulation have been applied in the evaluation of these patients.[23,24] Thus, comparison of studies in young patients is difficult, due to both differing patients subgroups and stimulation protocols. Based on this study, we would predict low sensitivity for programmed stimulation studies restricted to S_3 protocols. Similar results, suggesting increased sensitivity with aggressive protocols, have been reported by the Cooperative Study of Ventricular Arrhythmias in Postoperative Tetralogy of Fallot.[25]

The induction of VF in 5 cases during this study preceded by coupling intervals ≤190 ms deserves comment. As no patient had induction of sustained VT with

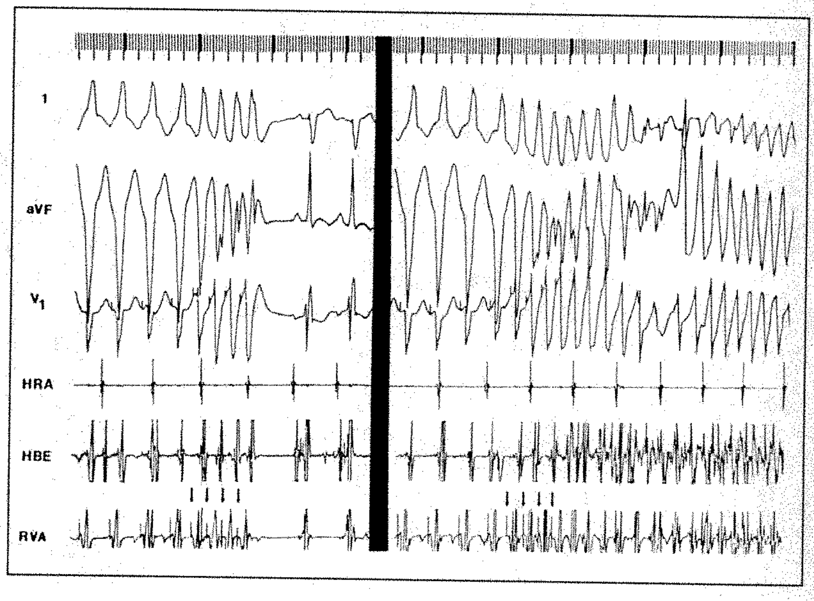

FIGURE 3. Induction of ventricular fibrillation. *Left,* 4 extrastimuli with coupling intervals ≥200 ms result in no abnormal ventricular response. *Right,* S_4 to S_5 interval was decreased from 200 to 180 ms with induction of rapid polymorphic ventricular tachycardia degenerating to ventricular fibrillation as a response. HBE = His Bundle electrogram; HRA = high right atrium; RVA = right ventricular apex.

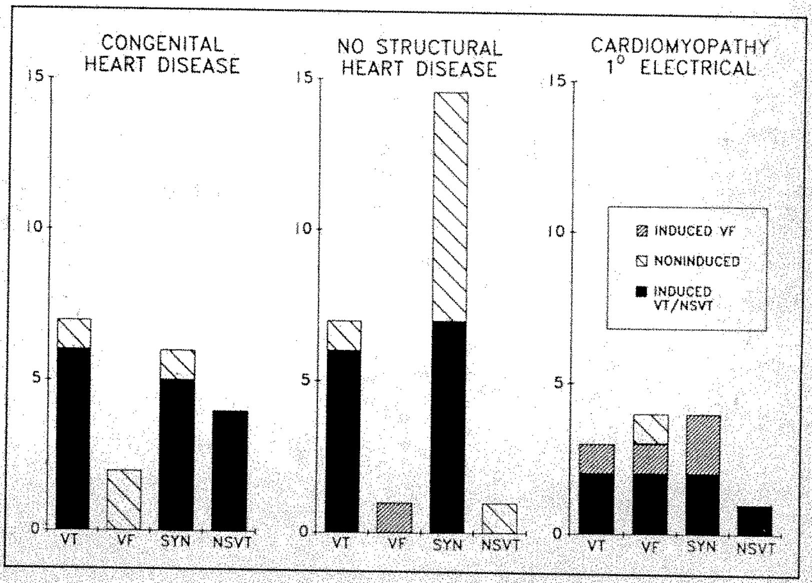

FIGURE 4. The frequency of ≥6 beats of nonsustained ventricular tachycardia (VT) as a response to programmed stimulation, plotted as function of the type of heart disease and presenting arrhythmia. Of the 31 patients with structural heart disease, 26 tested positive by this criterion. Fifteen of 17 patients with clinical sustained VT and 5 of 6 with nonsustained VT tested positive. Seven of 15 syncope without identifiable heart disease patients also tested positive when nonsustained VT was defined as the end point of stimulation. Abbreviations as in Figure 1.

coupling intervals <190 ms, it is possible that a lower limit of coupling intervals may exist, below which the specificity of responses is minimal.[26] However, the limited number of patients in this study preclude firm conclusion.

Responses to programmed ventricular stimulation: The induction of sustained monomorphic VT appears to be clinically significant in the young, even with stimulation incorporating up to 4 extrastimuli. Of the 18 patients with inducible sustained VT, 12 had clinical documentation of the arrhythmia and the other 6 had a presentation compatible with this diagnosis. In addition, the induction of monomorphic sustained VT in young patients appears to be a reproducible response, as in adults.[13,27]

The clinical significance of polymorphic VT or VF is less certain. In the survivor of aborted sudden death, these responses may correlate with prognosis.[28] However, in the absence of clinical correlation, or as a response to brief coupling intervals, the significance of such responses are uncertain.[29]

Two end points of programmed stimulation were evaluated in this study: sustained VT and nonsustained VT or VF. Although the use of sustained VT as a positive response limits sensitivity, the use of S_4 or S_5 protocols may result in false positive responses if nonsustained VT is accepted as significant.[30] Nonsustained VT may represent a positive response to less aggressive protocols in the young, although we did not address this specific question.

Prospective studies are required to define the relation of induction of nonsustained and sustained VT to future events. Sensitivity is the primary issue in patients with documented sustained VT and the use of aggressive programmed stimulation appears warranted. Conversely, specificity is paramount when patients without documented VT undergo electrophysiologic study.[31] In either subset of patients, the aggressiveness of the stimulation protocol and interpretation of results may need to be predicated on the specific clinical issue being addressed.

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Long-Term Follow-Up in Patients with Incessant Ventricular Tachycardia

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Seventeen patients with coronary artery disease, idiopathic dilated cardiomyopathy or no organic heart disease who presented with incessant ventricular tachycardia (VT) were studied and followed for a mean period of 51 ± 35 months. In these patients the incessant VT included ≥3 episodes of sustained VT at a rate of ≥120 beats/min and frequent episodes of nonsustained VT over a 24-hour period. No patient had electrolyte disorder, prolonged QT interval, drug-induced arrhythmia or myocardial infarction <2 weeks old. Six patients died within 27 months of follow-up; 4 from sudden death and 2 from acute myocardial infarction. Three of the 11 surviving patients had remission of their VT within 1 week after the diagnosis of incessant VT. In 3 other patients in whom antiarrhythmic drugs were discontinued during follow-up because of adverse effects of the drugs or other medical reasons, 2 were found in remission. In the remaining 5 alive patients, deliberate attempts were made to discontinue the antiarrhythmic drugs; 4 of these patients were found in remission when the drugs were discontinued. Thus, 9 of these patients (53%) with incessant VT had remission over a mean follow-up of 55 ± 34 months after discontinuation of the antiarrhythmic drugs. The probability of remission in patients surviving incessant VT warrants trials of discontinuation of antiarrhythmic drugs in these patients.

(Am J Cardiol 1990;66:831–836)

Incessant ventricular tachycardia (VT) presents a challenge to clinicians because the patients are frequently incapacitated and because there is a compelling reason to suppress the arrhythmia quickly. The prevailing practice is that, similar to sustained VT,[1,2] once drug treatment of incessant VT is initiated, proved effective and without serious adverse effects, no attempts are made to stop the drug in order to find out if the patients with incessant VT are in remission. Our experience in treating patients with incessant VT indicates that a significant percentage of these patients in whom antiarrhythmic drugs are discontinued do not have VT any longer during long-term follow-up. This finding has modified our treatment approach for these patients.

METHODS

Patients: Seventeen patients were admitted to the University of Illinois Hospital and West Side Veterans Administration Medical Center between January 1977 and December 1987 with incessant VT that fulfilled the following arbitrary criteria: (1) Frequent sustained and symptomatic episodes of VT (≥3 episodes in 24 hours) occur in these patients. Sustained VT is defined as VT lasting >30 seconds or causing hemodynamic compromise. (2) In between episodes of sustained VT, there are frequent episodes of nonsustained VT (≥3 ventricular ectopic beats in succession) and single or paired ventricular ectopic beats resulting in total ventricular ectopic beats in 24 hours more than total sinus beats. (3) The incessant period lasts >24 hours. (4) Rates of VT exceed 120 beats/min. (5) Patients with electrolyte disorder, prolonged QT interval (QTc >0.44 second), suspected drug-induced arrhythmias or myocardial infarction <2 weeks old were excluded from the series. Special efforts were made in these patients to rule out drug-induced arrhythmias by discontinuing all antiarrhythmic drugs for ≥24 hours (or ≥4 elimination half-lives) and by confirming the persistence of incessant VT despite discontinuation of the drugs. In addition, in 3 patients who had been treated with procainamide and in 4 patients who had been treated with procainamide and lidocaine by the referring physicians, procainamide levels obtained at the time of admission of these patients were <3.0 μg/ml and lidocaine levels were <1.0 μg/ml. In all 6 patients receiving digoxin before the episode of incessant VT, the dose of the drug had been stable for at least 1 month and the level at the time of hospital admission was <2.0 ng/ml.

Evaluation of patients: All patients were monitored electrocardiographically during the entire period of in-

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TABLE I Clinical Characteristics

Pt.	Age (yr) & Sex	Anatomic Cardiac Diagnosis	Symptoms	Duration of Preincessancy	Duration of Incessant VT (Days)	LVEF (%)	Follow-Up (mo)	Outcome
1	59M	CAD	P, S	3 Weeks	2	43	101	R (20 mo)
2	60M	CAD	P, D	1 Month	2	34	97	R (97 mo)
3	65F	CAD	P, CA	5 Years	3	48	13	Died
4	68M	CAD	P	2 Months	1	21	12	Died
5	69F	CAD	P, S	6 Years	2	66	23	Died
6	71M	CAD	P, CA	3 Years	2	17	22	Died
7	74M	CAD	P	0 Day	3	58	16	R (13 mo)
8	82M	CAD	P, D, S	1 Year	2	47	41	R (38 mo)
9	17F	IDC	P	2 Months	2	47	87	R (59 mo)
10	30F	IDC	P, D	7 Days	3	48	18	R (14 mo)
11	31M	IDC	P	15 Years	1	41	78	NR
12	41F	IDC	P	2 Years	2	47	67	NR
13	72M	IDC	P	5 Months	3	31	6	Died
14	21M	O	P	6 Months	1	50	57	R (52 mo)
15	27F	O	P	2 Years	1	56	102	R (102 mo)
16	41M	O	P, D	1 Year	3	67	96	R (96 mo)
17	68M	O	P, D	3 Years	1	59	27	Died

CA = cardiac arrest; CAD = coronary artery disease; D = dizziness; IDC = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NR = not in remission, still taking antiarrhythmic drugs; O = no organic heart disease; P = palpitations; R = in remission, not taking antiarrhythmic drugs (numbers in parentheses are the length of time in months the patient was in remission); S = syncope; VT = ventricular tachycardia.

cessant VT. Holter monitoring was also done before and after administration of oral antiarrhythmic drugs. Thirteen patients had treadmill testing and all underwent gated radionuclide ventriculography to measure left ventricular ejection fraction. Cardiac catheterization and coronary angiography were performed in 15 patients. Programmed ventricular stimulation was performed in all patients according to a previously described protocol,[3] in 14 patients when incessant VT had stopped and in 3 during the period of incessancy. In 8 patients who did not have inducible sustained VT with this protocol, programmed ventricular stimulation was repeated during intravenous isoproterenol infusion (1 to 4 μg/min). No cardiac surgery or transcatheter ablation was performed in any of these patients during the follow-up.

After explaining the investigative nature of the protocol including the risks and benefits and after signing an informed consent, asymptomatic patients who had no sustained or nonsustained VT during the follow-up while taking antiarrhythmic drugs were hospitalized, electrocardiographically monitored and had the drugs discontinued. Electrocardiographic monitoring was continued for ≥5 elimination half-lives of the drug. In 1 patient in whom amiodarone was discontinued, the patient was electrocardiographically monitored for 10 days. Treadmill stress testing, Holter monitoring, programmed ventricular stimulation were performed in all patients at the end of the electrocardiographic monitoring period. The patient who had received amiodarone was rehospitalized for a repeat of the aforementioned tests 6 months after discontinuation of the drug.

Remission was suspected if, on discontinuation of the antiarrhythmic drugs for >5 elimination half-lives, no recurrence of sustained or nonsustained VT occurred and a previously inducible sustained VT could no longer be induced by programmed ventricular stimulation. The patients were considered in remission if they were free of symptomatic ventricular arrhythmias for ≥12 months of follow-up and repeated Holter monitoring showed neither sustained nor nonsustained VT.

RESULTS

Patient characteristics: Table I lists the clinical characteristics of the 17 patients. In this table, each patient is indicated by a number that will be used throughout. At the time of the appearance of the incessant VT, the patients were 17 to 82 years of age (mean 53 ± 21). Six patients were women and 11 were men. Five patients had a diagnosis of idiopathic dilated cardiomyopathy on the basis of low left ventricular ejection fraction (normal 55 to 70%) and the absence of significant valvular lesions on cardiac catheterization or coronary artery obstruction on coronary angiograms. Eight patients had a diagnosis of coronary artery disease on the basis of history and electrocardiographic evidence of prior myocardial infarction and/or significant coronary artery obstruction associated with angina pectoris. Four patients had no diagnosable organic heart disease on the basis of normal cardiac findings during clinical examination, absence of significant coronary artery obstruction or valvular lesions during cardiac catheterization, and normal left and right ventricular ejection fractions by radionuclide or contrast angiograms. The average left ventricular ejection fraction in the 17 patients was 46 ± 14%.

All patients except patient 7 had a history of symptomatic ventricular premature beats or nonsustained VT 7 days to 15 years before onset of incessant VT. Patients 5, 8 and 11 also had previously documented sustained VT. Patient 7 had incessant VT as the initial presentation of the ventricular arrhythmias. Palpitations were reported by all patients. Three patients had syncopal episodes and 2 were successfully resuscitated from an episode of cardiac arrest. The duration of incessant VT before the episodes of sustained VT was controlled

TABLE II Characteristics of Sustained Ventricular Tachycardia

Pt.	Bundle Branch Block Pattern	Axis	CL (ms)	Inducibility	Response to Rapid Ventricular Pacing	Initial Drug Suppression
1	R	I	360	0	0	Amiodarone
2	R	R	460	0	OS/T	Procainamide
3	L	R	340	+	0	Aprindine
4	L	L	500	0	OA	Aprindine, disopyramide
5	L	L	340	+	OS/T	Aprindine
6	R	R	360	0	OS	Amiodarone
7	R	R	490	—	0	Encainide
8	R	R	320	+	OS/T	Lidocaine, procainamide
9	L	R	360	0	OS	Procainamide
10	L	R	400	—	OS/T	Encainide
11	L	L	400	0	OS/T	Disopyramide, aprindine
12	L	R	500	+	OA/T	Propranolol, mexiletine
13	R	I	380	0	OS/T	Aprindine
14	L, P	R	400	0	OS/T	Quinidine
15	L	N	490	0	OS	0
16	L	N	280	—	OS/T	Lidocaine
17	R, P	R	350	0	0	Amiodarone

CL = cycle length; I = indeterminate; L = left; N = normal; OA = overdrive acceleration; OS = overdrive suppression; P = polymorphic; R = right; T = termination.

with antiarrhythmic drugs or it spontaneously ceased (range 1 to 3 days, mean 2.0 ± 0.8, Table I).

Thirteen patients underwent treadmill testing: in 3 while recurrent episodes of nonsustained VT and frequent ventricular ectopic beats were still occurring and in the other 10 when episodes of sustained or nonsustained VT were suppressed by drugs or had spontaneously disappeared. During exercise, VT was suppressed in 2 of the 3 patients with episodic nonsustained VT. Sustained VT at a rate of 180 beats/min was induced during exercise in the other patient. There was no VT induced during treadmill testing in the remaining 10 patients including 2 patients with a history of exercise-induced VT.

All except 2 patients (patients 6 and 8) underwent cardiac catheterization and coronary angiography. The 4 patients with no organic heart disease in Table I had completely normal findings. Six patients (patients 1 to 5 and 7) had 1 to 3 significant (>70%) coronary artery narrowings. In addition, 4 patients (patients 1, 3, 4 and 7) had significant regional wall motion abnormalities.

Electrophysiologic characteristics of ventricular tachycardia: Table II lists the important electrophysiologic characteristics of the sustained VT. The cycle lengths during sustained VT ranged from 280 to 500 ms (mean 392 ± 67). Figure 1 illustrates the rhythm strip of patient 10 during the period of incessancy. During this period, episodes of sustained and nonsustained VT were interspersed by sinus beats and ventricular ectopic beats. Rapid ventricular pacing during spontaneous or induced sustained VT at a rate faster than the rate of the VT resulted in overdrive suppression, defined as prolongation of VT cycle length by >50 ms, in 3 patients, overdrive suppression or termination in 8 patients, overdrive acceleration in 1 patient, overdrive acceleration followed by termination in 1 patient and no effects in 4 patients. Programmed ventricular stimulation in the drug-free state showed that 4 of these patients had inducible sustained VT. Three of these patients had coronary artery disease and 1 patient had idiopathic dilated cardiomyopathy.

On 77 different occasions, various drugs including procainamide, quinidine, disopyramide, lidocaine, mexiletine, tocainide, flecainide, encainide, propranolol, amiodarone, bretylium, verapamil and aprindine were tested in an attempt to control spontaneous sustained VT or to prevent induction of sustained VT. The average number of drugs used in each patient was 4.5 ± 2.2 drugs (range 1 to 7 drugs). Among the most frequently effective drugs were aprindine which controlled the tachycardia in 5 of 6 drug testings, procainamide in 3 of 8, disopyramide in 2 of 8 and encainide in 2 of 4. In 3 patients (patients 1, 6 and 17) amiodarone was begun when other drugs proved to be ineffective. In these patients episodes of sustained VT were not seen after the administration of amiodarone.

Follow-up: The follow-up period, measured from the time of diagnosis of incessant VT to the last contact with the physician or to the time of death, ranged from 6 to 102 months (mean 51 ± 35, Table I). All patients alive at the end of the follow-up period had been followed for >1 year. During follow-up 6 patients (35%) died: 4 suddenly and 2 from acute myocardial infarction.

The outcome of other patients that were alive at the end of their follow-up is shown in Table I. Spontaneous remission occurred in patients 2, 15 and 16 within 1 week after the diagnosis of incessant VT. These patients were found to be in remission during baseline Holter and electrophysiologic studies. Follow-up Holter monitorings and treadmill stress tests in these patients followed for 97, 102 and 96 months revealed only infrequent single ventricular premature beats.

Incessant VT was suppressed by procainamide in patients 8 and 9. In addition, the previously inducible sustained VT in patient 8 was no longer inducible after intravenous infusion of procainamide. On the basis of the previously mentioned results, patients 8 and 9 were given oral procainamide therapy. Patient 8 developed new signs and symptoms of congestive heart failure when he was taking procainamide, 4 g/day. Because of these findings, procainamide was discontinued 3 months after the diagnosis of incessant VT. In patient 9, procainamide had to be discontinued 28 months after the diagnosis of incessant VT to avoid undesirable side effects to her fetus during her pregnancy. These 2 patients were found to be in remission during 38 and 59 months after procainamide had been discontinued.

Patient 12 continued to have palpitations due to sustained VT at a rate of 100 to 120 beats/min while she was taking mexiletine and propranolol. Because of lack of complete control of symptom by this regimen, an empirical trial of flecainide was begun. The patient continued to have episodes of mild palpitation and dizziness with flecainide. This patient did not go into remission.

From the aforementioned data, it became clear that, retrospectively, of the 6 surviving patients in whom antiarrhythmic drugs were discontinued for a variety of reasons, 5 were in remission. On the basis of these findings, attempts were made to discontinue the antiarrhythmic drugs in the remaining 5 surviving patients (patients 1, 7, 10, 11 and 14). These patients had been asymptomatic with amiodarone (patient 1), encainide (patients 7 and 10), aprindine (patient 11) and quinidine (patient 14). Patients 7, 10 and 14 who had been asymptomatic with antiarrhythmic drugs for 3, 4 and 5 months did not have spontaneous or induced sustained VT after the discontinuation of the drugs. These patients remained asymptomatic without any antiarrhythmic drugs for 13, 14 and 52 months, respectively. Patient 1 who had been asymptomatic with amiodarone for 81 months after the diagnosis of incessant VT was admitted after amiodarone had been discontinued for 1 week. Stress testing and programmed ventricular stimulation when amiodarone had been discontinued for 17 days failed to show spontaneous or inducible sustained VT. A repeat of studies 6 months later confirmed that the patient was in remission. The patient remained asymptomatic without amiodarone during a follow-up of 20 months. Patient 11 had aprindine discontinued 64 months after the diagnosis of incessant VT. VT recurred on the fifth day after the drug had been discontinued. Aprindine was restarted and the patient continued to be asymptomatic.

DISCUSSION

We describe the long-term course of a group of patients with diverse cardiac conditions who presented with a malignant ventricular arrhythmia. The ventricular arrhythmia in these patients was classified as incessant VT for lack of a more accurate term, although there has been no consistency in the definition of this term.[4–7] For example, Garson et al[4] defined incessant VT as the presence of VT occurring in $>10\%$ of a 24-hour monitoring period, whereas Lemery et al[5] defined incessant VT as VT present for at least one-half of each of 3 days. Other investigators described repetitive VT that represents episodes of VT, mostly nonsustained, interspersed by short periods of sinus rhythm.[8–18] In this study, we described patients that had a more malignant condition, because we have included in our inclusion criteria the presence of ≥ 3 episodes of symptomatic sustained VT during a period of 24 hours. Paradoxically, however, despite the malignant course of this condition in some patients, we found that 9 of 11 surviving patients went into remission during the follow-up. Most of these patients who went into remission had ventricular arrhythmia before the incessant VT and were completely "cured" of the arrhythmia during a long-term follow-up.

In this study the time of onset of remission in these patients could not be accurately determined. In 3 patients, remission was detected within 1 week after the episode of the incessant VT. In other patients, antiarrhythmic drugs were discontinued at a later time because of certain medical reasons or on deliberate attempts by the investigators to determine whether the patients were in remission. It is possible that these patients might have gone into remission much earlier than the time we actually discontinued the antiarrhythmic drugs. For example, during hospitalization for the incessant VT, when drug testing was performed in these patients, remission might have been interpreted as success-

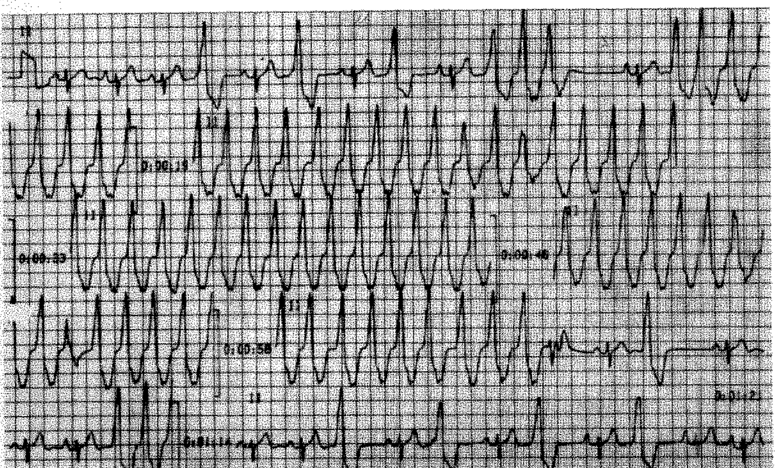

FIGURE 1. Rhythm strip (lead II of the electrocardiogram) of patient 10 during the period of incessancy. During this period, episodes of sustained VT lasting about 1 minute (from the *end of upper trace* to the *fourth trace*) and nonsustained VT *(upper trace)* are interspersed by sinus beats and ventricular ectopic beats.

ful suppression of the incessant VT by an antiarrhythmic drug. The low incidence of inducibility of VT (only in 4 patients in the series) by programmed ventricular stimulation might suggest abnormal automaticity as the underlying mechanism of VT in these patients.[18] However, another likely explanation for the low incidence of inducibility is that some of our patients were already in remission at the time of programmed ventricular stimulation.

In previous studies other investigators have described changes in manifestation of various types of ventricular arrhythmias. Remission has previously been reported in patients with repetitive VT.[10-12,18] In addition, 1 of 11 patients with incessant VT reported by Lemery et al[5] developed a "spontaneous cure." The reported incidence of remission in these patients, however, might be lower than the true incidence, because no attempt was made to discontinue previously effective antiarrhythmic drugs. Changes in frequency of single and paired ventricular ectopic beats and VT over time have also been reported.[19-21] Changes in the results of programmed ventricular stimulation have also been reported.[22,23] Also in this context, a follow-up study of patients that received automatic implantable defibrillators showed that in >50% of patients who had received the device, electrical discharge never occurred or occurred because of events other than ventricular arrhythmias.[24] The interpretation of this may be that some of these patients were probably in remission and may not have needed the expensive device.

Clinical implications: In current medical practice, physicians who initiate antiarrhythmic drugs in patients with ventricular arrhythmias would continue the drugs indefinitely unless adverse effects occur, the drugs are no longer effective or other medical reasons dictate discontinuation of the drugs. In malignant ventricular arrhythmias, there is an obvious reluctance for a physician to try to discontinue antiarrhythmic drugs, because of concern that the recurrence of the arrhythmias may prove fatal. For example, Graboys et al[25] reported a high recurrence rate of malignant ventricular arrhythmias in patients with sporadic VT when drugs that proved effective in suppressing the ventricular premature beats were discontinued. However, one could make a strong case for stopping antiarrhythmic drugs that are clearly not needed. Most antiarrhythmic drugs have multiple side effects. Even when these drugs show a lack of intolerable side effects initially, they may become more apparent and intolerable during follow-up.[26,27] The most dreaded side effect is worsening of the arrhythmia (proarrhythmia), a potentially lethal condition. For example, in the recent Cardiac Arrhythmia Suppression Trial, 2 potent antiarrhythmic drugs (flecainide and encainide) used to treat ventricular ectopic beats after myocardial infarction have been associated with increased mortality.[28] For the previously mentioned reasons, patients taking antiarrhythmic drugs should be followed closely with clinical examinations and laboratory tests that may not be needed for patients not taking antiarrhythmic drugs. The price of the drugs together with the more frequent medical visits and laboratory tests can be translated into higher medical costs for these patients.

In the patients reported here we were able to discontinue antiarrhythmic drugs without any subsequent adverse sequelae. The appearance of incessant VT has been our clue as to whether remission is a possibility. The current study shows that much still needs to be learned on the proper initiation and discontinuation of antiarrhythmic drugs for malignant arrhythmias.[29] Based on the results of this study in a limited number of patients with incessant VT and diverse cardiac conditions, we recommend that a patient with incessant VT not associated with acute myocardial infarction or other reversible causes be treated with an antiarrhythmic drug during the acute episode. The patient should then be discharged on the antiarrhythmic drug proved to be effective during hospitalization. During follow-up, if the patient remains asymptomatic and free of documented VT with the drug, a trial of discontinuation of the drug in the hospital and in a monitored area should be performed to determine if the patient is in remission. If on discontinuation of the drug there is no evidence of existing malignant ventricular arrhythmias, close follow-up should then be continued on an outpatient basis. Until further study in a larger population, it is not clear which patients will or will not go into remission. It is also unclear when remission in patients with incessant VT most commonly occurs. Our initial impression is that patients with a brief history of ventricular arrhythmia before the incessant VT probably have a higher chance for remission during follow-up.

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The Nuclear Pacemaker: Is Renewed Interest Warranted?

Victor Parsonnet, MD, Alan D. Berstein, EngScD, and Gershon Y. Perry, MD

From 1973 through 1987, 155 radioisotope-powered "nuclear" pacemakers were implanted in 132 patients at the Newark Beth Israel Medical Center. The longevity of the first 15 devices, all of which were fixed-rate (VOO) pacemakers, was significantly better than that of 15 lithium-chemistry demand (VVI) pacemakers used as control devices (p = 0.0002). Of the entire cohort of 155 nuclear pacemakers, 136 were VVI devices and 19 were VOO units. The patients with VOO pacemakers needed reoperations more often than did those with VVI pacemakers, chiefly for mode change (p <0.001). Power-source failure was observed in only 1 case, but 47 nuclear pacemakers were removed for other reasons, including component malfunction (15 units), mode change (12 units), high pacing thresholds (8 units) and lead or connector problems (5 units). The actuarial survival at 15 years was 99% for power sources and 82% for the entire pacing systems (pulse generators plus leads). The frequency of malignancy was similar to that of the population at large and primary tumor sites were randomly distributed. Deaths most commonly were due to cardiac causes (68%). Thus, nuclear pacemakers are safe and reliable and their greater initial cost appears to be offset by their longevity and the resulting decrease in the frequency of reoperations. It is reasonable to suggest that further use be made of long-lasting nuclear power sources for modern pacemakers and other implantable rhythm-management devices.

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The radioisotope-powered "nuclear" pacemaker pulse generator was introduced almost 20 years ago to meet an indisputable need for a reliable, long-lived power source for implantable pacemakers. Despite a favorable experience with their use, very few have been implanted since 1983 and all manufacturers except 1 have ceased production.[1-11] In 1988, a new dual-chamber (DDD) version became available after its use was approved by the Nuclear Regulatory Commission (NRC) and the US Food and Drug Administration (FDA). (Pacing modes referred to in this report [DDD, VOO, VVI, VAT, VVIR] are designated according to the North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group Generic Code[12]). This has prompted a review of our experience with the earlier devices and a reappraisal of nuclear power sources for implanted devices in the context of today's pacing innovations. Because the mercury-zinc cells used in the earliest implanted pacemakers lasted for such a short time, typically about 18 months, the need for a new power source was evident. Various manufacturers then worked on the development of radioisotopic power supplies for implanted pacemakers, including Numec (later Arco Medical Products Company), Biotronik, Cordis, Coratomic and Medtronic in association with the Alcatel Company in France. Several isotopes were evaluated for feasibility and safety in this application. Eventually, plutonium-238 was selected as the isotope of choice. The thermal energy (heat) of the isotope was transformed into electrical energy through a bismuth-telluride thermopile, forming a thermoelectric generator. (Other types of energy sources also had been considered, such as the β-emitting promethium-147 source developed by Biotronik, but only the plutonium versions achieved any level of clinical acceptance.[10,13,14])

The first nuclear pacemaker was implanted in France in April, 1970.[3,15] None was implanted in the United States until April 1973, when 15 were implanted at this institution and 1 was implanted in Bethesda.[16] Since then, >3,000 have been implanted worldwide. A final report on that entire experience has never been published, although some results can be found in pacemaker manufacturers' in-house reports (additional [unpublished] data from Telectronics/Cordis Pacing Systems).[5,17] The results of our own experience with nuclear pacemakers during the first 10 years were reported in 1984.[18] This report describes our experience with our first 132 patients followed over a period of 15 years and calls attention to a new radioisotopic dual-chamber (DDD) pulse generator.

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TABLE I Nuclear Pulse Generators Used in the Study

Pacemaker and Mode	Pacing Mode	Primary Implants	Replacements	Totals
Cordis 184 A/B	VVI	45	14	59
Medtronic 9000A	VVI	35	2	37
Coratomic C100/C101	VVI	19	4	23
ARCO NU-5F	VOO	19	0	19
ARCO NU-5D	VVI	14	3	17
Totals		132	23	155

TABLE II Comparison of Group I and Control Group

	Control Subjects	Group I	
No.	15	15	
Pacing mode	VVI	VOO	
Pulse generators/patient			
Mean (SD)	2.9 (1.6)	1.4 (0.5)	$p < 0.008$
Range	1–7	1–2	
Pulse-generator longevity (months)			
Mean (SD)	29.6 (16)	105.8 (67)	$p = 0.0002$
Range	3–61	24–180	
Pulse-generator failures			
Power-source depletion	13 (86%)	0	
Component	1	0	
Infection	1	0	
Patient status			
Alive	4	9	(NS)
Died	8	5	(NS)
Lost to follow-up	1		

NS = not statistically significant.

TABLE III Explantations of Nuclear Pulse Generators

	Group I (n = 15)				Group II (n = 132)				
Complication*	No.	Explanted	New Nuclear	New Lithium	No.	Explanted	Same Nuclear Reimplanted	New Nuclear	New Lithium
Lead malfunction	7[†]	2	1	1	50[†]	8	42	4[‡]	4[§]
Threshold rise	0	—	—	—	19	7	0	3	5
Component failure	0	—	—	—	15	15	0	9[‖]	5
Mode change	3[¶,**]	3	1	2	10[††,**]	10[‡‡]	—	2	8
Twitch or EMI	0	—	—	—	7	4	—	3	4[§§]
Extrusion or infection	1	1	1	0	5	3	0	1	1[‖‖]
Miscellaneous	0	—	—	—	3	0	3[¶¶]	—	—
Power-supply failure	0	—	—	—	1	1	—	1	—
Totals***	11	6	3	—	110	48	—	23	—

* Only primary reason listed—those with secondary problems are annotated.
[‡] 2 also required mode change; [¶] 3 had incidental problems, unspecified; [§] 2 also required mode change; [‖] 1 also required mode change; [‡‡] 2 also had pocket twitch; [††] 6 had incidental problems, unspecified; ** 2 of 4 additional VOO pacemakers also needed mode change; [§§] 1 also required mode change; [‖‖] 1 explanted elsewhere, not replaced; [¶¶] 2 pulse generators repositioned elsewhere; 1 defunctionalized lead extracted; [†] including 5 lead fractures, 4 in group I; *** due to overlapping conditions, not all columns included in totals.
EMI = electromagnetic interference.

METHODS

Patients were selected for nuclear-pacemaker implantation in accordance with a protocol established by the Atomic Energy Commission (AEC), the NRC and the FDA. They were to be relatively young and free of associated diseases that might limit their survival, so that they had a life expectancy of ≥10 years. They also were to agree to abide by the follow-up schedule, which did not differ significantly from standard methods, and to agree that the pacemaker would to be returned to the AEC in the event of explantation or death.

There were 132 patients, 82 (62%) men and 50 (38%) women, mean age 49 years (range 5 to 76). Thirty-seven patients (28%) were <40 years old. The pacing mode was VOO (fixed rate) in the first 19 patients and VVI (demand) in the remaining patients. (The 8 nuclear pacemakers most recently implanted in 1989 were dual-chamber devices; these have not been included in this long-term analysis.)

Devices and implantation techniques: The implants were manufactured by 5 different companies (Table I) and incorporated plutonium generators of individualized design. The first Arco pacemakers were bulky; 32 mm thick and 120 g in mass. The Medtronic pulse generators were even heavier (170 g), but thinner (27 mm). The ovoid Coratomic unit was the smallest and had the most acceptable shape, but still was quite large by today's standards (61 g, 19 mm). All but the Medtronic pacemaker were unipolar systems. Because of our preference at the time for unipolar pacing, many of the bipolar Medtronic units were unipolarized by connecting an implantable ground plate to the anodal terminal, which added some bulk to the pacing system.

One hundred twenty-four implants were transvenous, with 70 pulse generators attached to new leads and 54 to existing ones. Eight were attached to epicardial leads, 4 new and 4 existing.

Indications for pacing: The electrocardiographic indications for pacemaker implantation were fixed or intermittent complete heart block (including symptomatic trifascicular block), present in 86 patients (65%), symptomatic sinus-node dysfunction in 25 patients (19%), and miscellaneous indications in 21 patients (16%), such as atrial fibrillation with varying degrees of atrioventricular (AV) block and sinus-node dysfunction with AV block.

Co-morbidities existed in 48 patients. Arteriosclerotic cardiovascular disease or cardiomegaly was present in 27 (20% of cases), congenital heart disease in 10 (8%), chronic obstructive pulmonary disease in 5 (4%), recent but apparently cured or relatively slow-growing malignancy in 4 (3%), and postoperative open-heart surgery in 3 (2%: aortic-valve replacement, mitral-valve replacement and ligation of the His bundle). Two patients (2%) had mild chronic renal failure and 2 had postmyocarditis cardiomyopathy. Twelve patients (9%) had 2 co-morbidities.

RESULTS

The patients were considered in 2 groups. Group I comprises the first 15 patients, all of whom received VOO (fixed-rate) Arco Nu-5F pulse generators; group II comprises *all* patients who received nuclear pulse generators, including those in group I. The 15 patients in group I were matched prospectively with 15 control subjects, all of whom received lithium-powered VVI (demand) units. At the time of the first implantations, VVI nuclear pacers were not available, a situation that lasted through the next 4 VOO implantations. (These have been described in more detail in a previous publication.[19]) Thus, although the patients were well matched, all of the nuclear-pacemaker group had VOO pacemakers, whereas all of the control subjects had VVI devices powered by lithium-iodide batteries.

Group I (nuclear VOO): The actuarial survival of the patients and the pulse generators is shown in Figures 1 and 2. The patient survival in the nuclear-pacemaker group was better, but the difference was not statistically

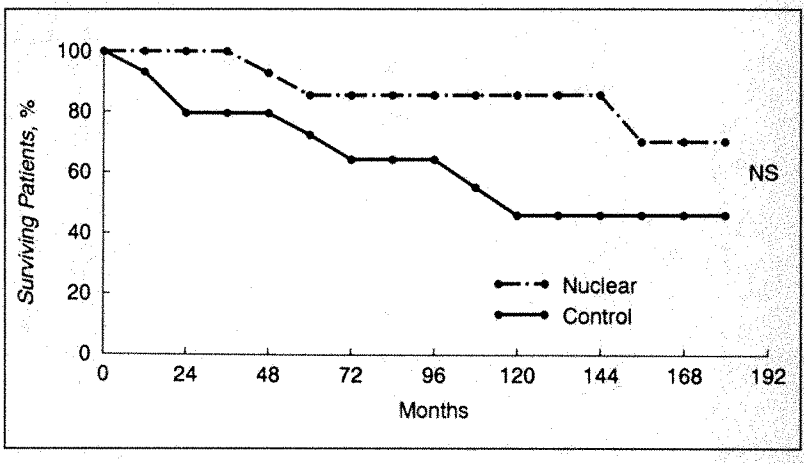

FIGURE 1. Cumulative actuarial survival of first 15 patients who received fixed-rate (VOO) nuclear pacemakers, compared with 15 control subjects who received nonnuclear VVI pacemakers. NS = difference not significant.

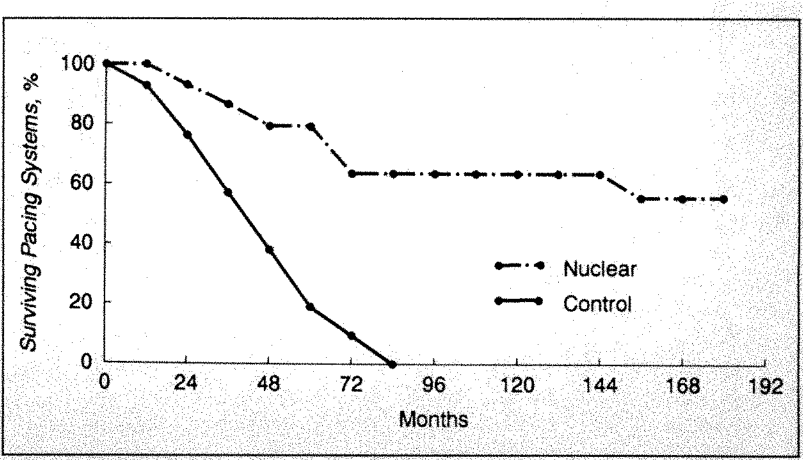

FIGURE 2. Cumulative survival of first 15 nuclear pulse generators, compared with 15 nonnuclear control pulse generators, reflecting the results of explantation for any reason.

TABLE IV Cumulative Survival of Nuclear Pulse Generators at 15 years, Grouped by Manufacturer

Manufacturer	Total (%)	Active (%)	Failed (%)	Withdrawn (%)	LFU
Medtronic	37 (24)	10 (27)	6 (17)	20 (54)	1
Cordis	59 (38)	29 (49)	7 (12)	20 (34)	3
Coratomic	23 (15)	11 (48)	3 (13)	8 (35)	1
Arco	36 (23)	14 (39)	2 (6)	18 (50)	2
Total	155 (100)	64 (42)	18 (11)*	66 (42)	7

* Survival = 82%.
LFU = lost to follow-up.

TABLE V Causes of Death

Cause	No.	%
Cardiac	19	47
Sudden death	9	22
Cancer	7	17
Pulmonary	2	5
CVA	1	3
Accidental	1	3
Unknown	1	3
Total	40	100

CVA = cerebrovascular accident.

significant. As listed in Table II, the mean longevity of the first 15 nuclear devices was 3.6 times that of the 15 lithium-powered VVI pacemakers used as control devices, none of which remains in use. Nine of the first 15 patients are alive; 5 (33%) still have their original pulse generators.

Three nuclear pulse generators were replaced with new nuclear units. Three were explanted primarily because of competition between the fixed-rate pacemaker stimuli and spontaneous cardiac activity, 1 being replaced with a new VVI nuclear unit and 2 with lithium-powered VVI pacemakers. Two of the control patients also eventually received nuclear pacemakers.

Group II (all nuclear pulse generators): One hundred fifty-five pacemakers were implanted in the 132 patients; 21 patients received a second nuclear pulse generator and 2 received a third (Table III). Five of the original 19 VOO units (3 of the first 15) were replaced primarily for change of mode. Seven additional pulse generators were replaced by lithium-powered dual-chamber devices (6 DDD and 1 VAT) and 2 by lithium-powered single-chamber adaptive-rate (VVIR) pacemakers. There was 1 power-source failure, but 64 nuclear pacemakers continue to function satisfactorily, with an actuarial survival of the pacemaker system of 82% at 15 years (Table IV and Figures 3 and 4).

Forty patients have died (Table V). The actuarial survival of the patients is shown in Figure 5. The most common cause of death was cardiovascular disease (68%), primarily cardiac disease (47%). There were also 9 sudden deaths (22%), presumably also cardiac in origin. Malignant tumors accounted for 7 deaths (17%).

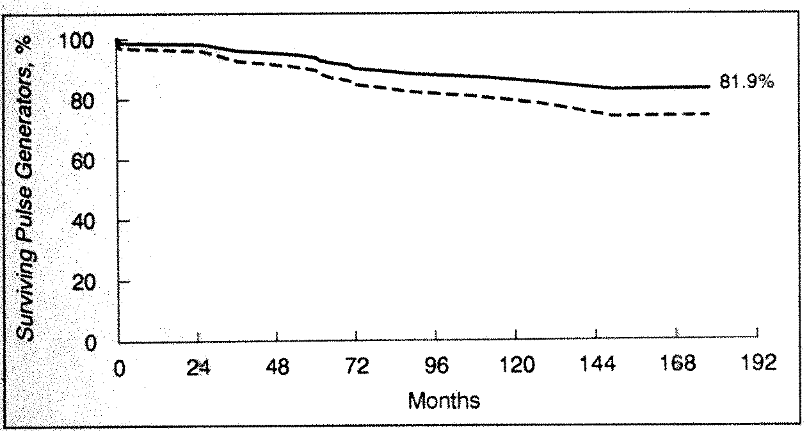

FIGURE 3. Cumulative survival of all 155 nuclear pulse generators considered in the study. *Dotted line* represents 90% confidence limit.

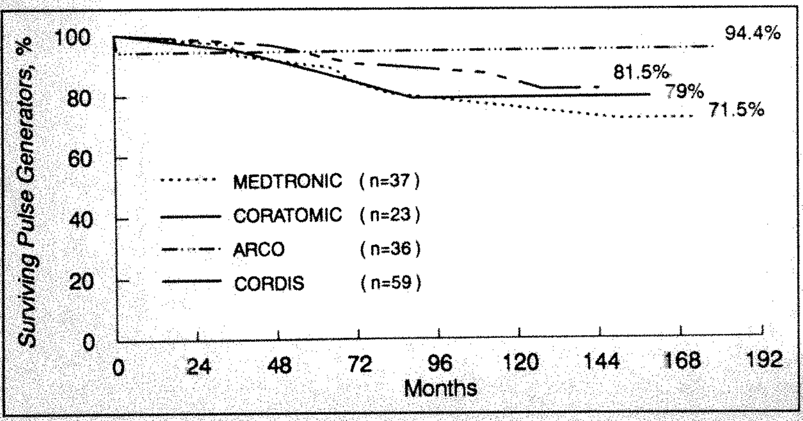

FIGURE 4. Cumulative survival of 132 nuclear pulse generators used in primary implants, grouped by manufacturer.

The existence of a malignancy was known at the time of implantation in 4 patients. The tumors had been considered either arrested or sufficiently slow-growing to justify the inclusion of these patients in the study. One of those 4 patients died of the tumor at 84 months, 1 died of cardiac disease and 2 are alive.

(Eight recently developed DDD pulse-generator models incorporating the same radioisotopic power supply, have been implanted within the past year ["Pulsar-N1," Biocontrol Technology, Inc.]. There have been no failures, complications or deaths.)

DISCUSSION

When radioisotopic pacemakers were first conceived, there was little doubt that they would perform as well as predicted, particularly with regard to the nuclear generator itself. The concept was relatively simple and had been extensively tested in earlier applications such as the "SNAP II" generator that was used to power ocean buoys. But one of the serious concerns of the NRC and FDA was the possibility that prolonged exposure to radiation would be carcinogenic. This concern persisted despite much theoretical and physical evidence that the radiation dosage was well within accepted limits.[19,20] For example, Webster[21] concluded in a report to the FDA that the radiation dose to the breast resulting from a single fluoroscopically-controlled replacement of a nonnuclear pacemaker by a skilled operator would be about 1.6 times as great as the estimated dose from 15 years of nuclear pacing (about 11.6 times as great with a less experienced operator). He also determined that, for a pectoral implant, the annual radiation dose anticipated from an isotopic pulse generator is 10% of the maximum permissible occupational dose of 15 REM per year. Thus, it is comforting to observe that there were only 7 new cases of cancer in 132 patients (5%), approximately what is to be expected in such a population during the period of the study.[22] Furthermore, there was no apparent relation between the location of the pulse generator and the site of origin of the neoplasms.

The nuclear pacemaker has lived up to its initial expectations and has met the objectives of the original protocols in that the actuarial survival at 10 years was >90% (at 15 years it was 82%), and that many such pacemakers continue to function normally even after 15 years. It is unlikely that there will be any new or unexpected complications. Because the radioisotope has a half-life of 87 years and the electronic circuits are expected to function normally through ≥1 half-life of the isotope, the pulse generators that remain active should continue to function for some years.

Many of the problems encountered with the first-generation (VOO) and second-generation (VVI) devices are not likely to be seen in future models, because component failures have become progressively rare in virtually all of today's pacemakers. Such reliability is evident in the periodic multicenter Bilitch Reports,[23] which have shown that many modern nonnuclear pulse generators exhibit an entirely normal function at 6 or 7 years. In this study, only 1 power-source failure occurred and that failure was due to a problem in the thermopile (not the isotope). The reliability of the nuclear power source is attested to by the actuarial survival of 99% at 15 years.

The pacemakers were replaced for a variety of reasons, most of which would not be seen in a new generation of devices. Competing rhythms and inappropriate modes would be avoided by a wider choice of noncompetitive modes that were not available to us years ago. The mix of pacing modes would then be the same as that of other modern pacemakers: 20 to 30% dual-chamber modes, 10 to 15% adaptive-rate modes (mainly VVIR) and almost all the rest VVI.[24]

Other drawbacks of the early nuclear pulse generators used in this study, such as excessive size, would not be seen in the future. Although nuclear pulse generators might be considered too large for some patients, the size of the 8 new nuclear dual-chamber devices implanted at this institution was found entirely acceptable by the patients who received them. Even if size were a consideration, would not most patients accept a pacemaker that will last 20 years without the need for replacement, rather than receive 2 or 3 pacemakers during the same time period along with the attendant cost of the surgery and the device, as well as the risk of complications?

Although it may be argued that future advances in technology might make desirable pacing functions avail-

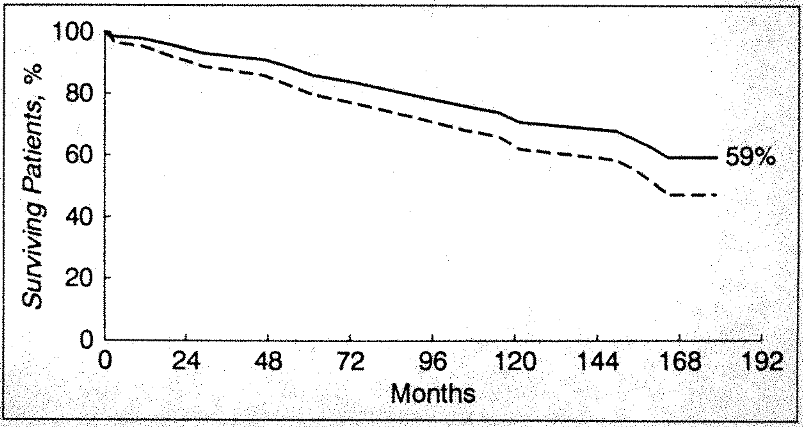

FIGURE 5. Cumulative survival of all 132 patients who received 1 or more nuclear pulse generators. *Dotted line* represents 90% confidence limit.

able well before a long-lived nuclear pacemaker would otherwise be replaced, it should be remembered that most modern pulse generators are software-based. With some such devices, extensive design modifications can be made and tested and a functionally new pacemaker can be "downloaded" noninvasively into a pacemaker that is already in place.

The paperwork required by the FDA certainly could be decreased, now that it has been shown beyond any reasonable doubt that there is no increased risk of malignancy in this group of patients.

Finally, the cost of pacing would be reduced. Although the first implants in 1973 were considerably more expensive than their mercury-zinc VOO or VVI counterparts, the relative freedom from reoperations in the long run made the cost of nuclear pacing considerably lower than that of conventional pacemakers. The dual-chamber nuclear pacemaker most recently implanted at this institution cost only $750 more than its lithium-chemistry counterpart. Some advanced pacemakers are also relatively power-hungry, because they incorporate circuitry for capabilities beyond simple pacing and sensing, all of which require electric power for their operation. Such capabilities include dual-chamber modes, rate-modulation schemes and automatic stimulation-threshold tracking (some of the newer lithium-powered pulse generators have been made *larger* than their predecessors to accomodate batteries of greater capacity, and some are even more expensive than the current nuclear pulse generator). Power from the nuclear source will not be exhausted by complicated circuits because the nuclear source is not a storage battery, but a thermoelectric generator whose available energy capacity is determined largely by the half-life of the isotope and does not depend upon the amount of current drawn by the circuit, provided that current does not exceed the conversion capabilities of the thermopile.

Based upon the positive results reported in this series of 132 patients over the past 16 years, it is our opinion that abandonment of the nuclear power source has been unwise and uneconomical. Others have agreed with this contention.[10] Only one manufacturer still has a few dual-chamber pulse generators on hand. It is doubtful that they will manufacture any more unless there is a reasonable chance that there will be a market (D. Purdy: Biocontrol Technology, Inc. [formerly Caratomic, Inc.], personal communication). It is hoped that changes in the attitude of the medical community will make it possible for them to reconsider.

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Effects of Metoprolol on Rest and Exercise Cardiac Function and Plasma Catecholamines in Chronic Congestive Heart Failure Secondary to Ischemic or Idiopathic Cardiomyopathy

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To define the effects of 2 months of metoprolol therapy on cardiac function, aerobic performance and sympathetic nervous system activity, metoprolol (75 to 100 mg/day) was administered to 10 patients with chronic congestive heart failure (CHF). Metoprolol was discontinued in 2 patients because of worsening CHF. In the remaining 8 patients, peak oxygen uptake increased significantly (14.8 ± 3.0 to 16.1 ± 2.5 ml/kg/min, $p < 0.05$) as did the oxygen pulse (9.0 ± 2.2 to 12.6 ± 1.8 ml/beat, $p < 0.02$). Resting heart rate (87 ± 18 to 62 ± 9 beats/min, $p < 0.05$) and peak exercise heart rate (133 ± 13 to 105 ± 30 beats/min, $p < 0.02$) were both reduced. Mean resting ejection fraction increased from 0.15 ± 0.06 to 0.25 ± 0.11 and peak exercise ejection fraction also tended to increase (0.19 ± 0.11 to 0.28 ± 0.15, difference not significant). Both resting plasma norepinephrine (613 ± 706 to 303 ± 142 pg/ml, $p < 0.05$) and epinephrine (71 ± 50 to 40 ± 21 pg/ml, $p < 0.05$) were reduced. Circulating lymphocyte β-adrenergic receptor number was unchanged (1,334 ± 292 to 1,344 ± 456 receptors/cell, difference not significant). It is concluded that metoprolol therapy is associated with improvements in rest and exercise ventricular performance and maximal aerobic capacity. These improvements are associated with a decline in resting sympathetic nervous system activity.

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Accumulating evidence suggests that β-adrenergic blocking agents improve the symptomatic status and possibly the survival of some patients with congestive heart failure (CHF) due to idiopathic dilated cardiomyopathy.[1–3] The mechanisms responsible for the observed improvements are largely undefined. During the course of CHF, increased sympathetic nervous system activity occurs,[4] which may be deleterious.[5] Moreover, there is loss of myocardial responsiveness to β-adrenergic agonists in patients with chronic CHF, which is correlated to the degree of β-adrenergic receptor downregulation.[6] The effects of metoprolol on sympathetic nervous system activity in CHF remains unexplored.

The purposes of the present investigation were to better define the effects of metoprolol on rest and exercise cardiac function, aerobic performance, sympathetic nervous system activity and lymphocyte β receptor numbers in patients with symptomatic CHF due to both ischemic and idiopathic causes. Patients with an ischemic etiology were included since they also exhibited a compensatory activation of the sympathetic nervous system.

METHODS

Patients: Patients were considered eligible for the study if they were <70 years of age, had symptomatic CHF for >3 months, had a left ventricular ejection fraction <0.40, and were clinically stable without a change in medical therapy for >4 weeks before the study. Patients were excluded if they had exertional or unstable angina, myocardial infarction within 3 months, active alcoholism, obstructive lung disease or asthma requiring therapy with bronchodilators, symptomatic peripheral vascular disease, advanced atrioventricular block or an inability to perform bicycle exercise testing because of neurologic or orthopedic disease.

Ten men (mean age ± standard deviation 59 ± 7) entered the study (Table I). Four patients met the criteria of New York Heart Association functional class II, and 6 patients were in functional class III. CHF was due to coronary artery disease in 6 patients (documented myocardial infarction and/or >70% stenosis at angiography) and to idiopathic cardiomyopathy in 4 patients. All subjects were in normal sinus rhythm.

Drug administration: After baseline studies, metoprolol was begun at a dose of 6.25 mg twice daily

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TABLE I Clinical Characteristics

Pt	Age (Yr)	Diagnosis	Duration of CHF (mo)	LVEF (%)	VO_2 Peak (ml/kg/min)	Resting NE (pg/ml)	Receptor Density (no./cell)	NYHA	Medications
1	69	IDC	66	14	14.2	450	1,769	III	Digoxin, furosemide, procainamide
2	61	IDC	12	17	14.0	250	1,394	II	Digoxin, furosemide
3	44	CAD	13	12	16.6	730	755	III	Captopril, furosemide, isosorbide dinitrate
4	50	IDC	160	5	12.0	680	523	II	Digoxin, furosemide
5	65	CAD	4	8	8.5	2,310	614	III	Amitriptyline, digoxin, furosemide
6	56	CAD	7	5	16.8	550	245	III	Furosemide, quinidine, digoxin captopril
7	56	IDC	7	20	18.2	380	888	II	Digoxin, furosemide
8	61	CAD	35	12	17.7	200	938	II	Digoxin, furosemide
9	64	CAD	30	10	15.2	310	1,256	III	Quinidine, digoxin, metolazone
10	62	CAD	14	26	14.0	270	3,061	III	Furosemide, digoxin, enalapril

CAD = coronary artery disease; IDC = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NE = arterialized norepinephrine; NYHA = New York Heart Association functional classification; VO_2 peak = peak exercise oxygen uptake.

(Lopressor® 25 and 12.5 mg scored tablets were provided by Ciba-Geigy, Summit, New Jersey), and each week thereafter the dose was increased by 6.25 mg/dose (12.5 mg/day up to a dose of 25 mg/day) until the maximal dose of 50 mg twice daily was achieved. Patients received <100 mg/day if their systolic blood pressure was <90 mm Hg or if their resting heart rate was <60 beats/min. The development of worsening CHF was treated with increased diuretics with further increments in metoprolol held until there was a resolution of clinical findings. Patients were withdrawn if there was persistent hypotension or worsening CHF despite these maneuvers. Baseline studies were repeated after 8 weeks of therapy.

Cardiopulmonary exercise test: After a 4-hour fast, each patient performed a familiarizing symptom-limited cardiopulmonary exercise test. A second test was performed just before initiating therapy to serve as the baseline. Testing was repeated at 8 weeks, 1 to 2 hours after oral metoprolol.

Patients exercised while seated upright on an electronically braked cycle ergometer. After a rest period of 5 to 15 minutes, the patients cycled for 4 minutes at "0" W (unloaded pedaling), and then the work rate was increased continuously at a rate of 10 W/min (ramp protocol), while pedaling frequency was maintained at 50 rpm. Breath-by-breath determinations of oxygen uptake (VO_2) were performed utilizing a Medical Graphics System 2010 cardiopulmonary exercise unit (Medical Graphics Corporation, St. Paul, Minnesota). Peak VO_2 was defined as the mean oxygen uptake measured during the last 15 seconds of exercise. Patients exercised until limited by dyspnea or fatigue. None experienced angina.

Plasma catecholamines, norepinephrine kinetics and lymphocyte beta-adrenergic receptors: Plasma catecholamines, norepinephrine kinetics and lymphocyte β-adrenergic receptor numbers were measured at baseline and at 8 weeks, 12 hours after the last dose of metoprolol. All samples were analyzed in a single batch.

All studies were performed in the recumbent position in the morning after an overnight fast. Medications were withheld on the morning of the study and patients were not allowed to smoke cigarettes or consume caffeine for 12 hours before the study. Intravenous catheters were placed in antecubital and hand veins. The hand was rested in a warming box (60°C) to obtain arterialized venous plasma. We have previously documented that plasma norepinephrine levels obtained from a hand vein placed in a warming box at 60°C correspond closely to simultaneously acquired arterial samples and therefore are referred to as "arterialized venous" plasma samples.[7] Arterialized plasma samples were obtained 30 minutes after catheter insertion for measurement of basal plasma norepinephrine and epinephrine levels.

Plasma norepinephrine appearance and clearance rates were measured using infusions of tritiated norepinephrine as previously described.[8] Blood samples for measurement of plasma catecholamines were collected and assayed by a single isotope enzymatic assay.[9]

Blood for lymphocyte β-adrenergic receptor studies was collected simultaneous to sampling for basal catecholamines. Lymphocytes were isolated on Ficoll-Hypaque gradients and all procedures were run at 4°C. Beta-adrenergic receptors and antagonist affinity (K_D) were quantified by Scatchard analysis of ^{125}I-iodocyanopindolol (specific activity 2,200 Ci/mmol; New England Nuclear Corp., Boston, Massachusetts) binding to lymphocyte membranes as have previously been described.[10]

Radionuclide angiography: Symptom-limited supine bicycle exercise radionuclide angiography was performed and analyzed as previously described.[11,12] Exercise began at a work load of 200 kpm and increased by 200 kpm every 4 minutes until exhaustion. At rest, during the last 30 seconds of each stage and at maximal exercise, 2.5 ml of arterialized venous blood was collected for catecholamines. Cardiac blood pool images were acquired for two 2-minute baseline periods at rest and then every 2 minutes during exercise. Blood pressure was measured every 2 minutes using an automated sphygmomanometer (Paramed model 9300, Paramed Technology, Inc., Palo Alto, California).

Statistical analysis: All results are expressed as mean ± standard deviation. The Wilcoxon Rank Sum test was used for comparisons of data obtained before and after treatment with metoprolol. Statistical significance was accepted at $p \leq 0.05$.

RESULTS

Drug tolerance and clinical effects: Eight patients completed the protocol. Seven received the maximal dose of 50 mg twice daily of metoprolol, whereas in 1 patient the dose was limited to 37.5 mg twice daily due to a resting heart rate of <60 beats/min. Two patients were intolerant of metoprolol and withdrawn from the study. One patient (no. 4) experienced hypotension, orthopnea and fatigue at 12.5 mg of metoprolol and one patient (no. 6) developed worsening pulmonary and peripheral congestion taking 50 mg/day, which required hospitalization. The dose of diuretics was transiently increased in 2 other patients who continued therapy, and there were no other changes in drug treatment.

Cardiopulmonary and radionuclide exercise studies (Table II): The heart rate at both rest and maximal exertion was significantly reduced with metoprolol (both $p < 0.05$). Systolic blood pressure increased modestly at rest (128 ± 10 to 139 ± 15 mm Hg, $p < 0.05$) and at maximal exertion (158 ± 26 to 170 ± 26 mm Hg, difference not significant) after metoprolol, whereas diastolic blood pressure was unchanged. The VO_2 peak averaged 14.8 ± 3.0 ml/kg/min before treatment and increased to 16.1 ± 2.5 ml/kg/min ($p < 0.02$) with metoprolol (Figure 1). An increase in VO_2 peak occurred in 7 patients and was >1 mg/kg/min in 4. The change in VO_2 peak was independent of changes in body weight (VO_2 peak = 1,196 ± 316 ml/min vs 1,291 ± 307 ml/min, $p < 0.02$). The maximal work rate increased from 90 ± 23 to 95 ± 21 W ($p = 0.06$). The mean oxygen pulse at maximal exertion, which is a measure of the amount of oxygen delivered per heart beat, increased by 40% (9.0 ± 2.2 to 12.6 ± 1.8, $p < 0.01$) (Figure 2).

The resting ejection fraction increased from 0.15 ± 0.11 to 0.25 ± 0.11 ($p < 0.05$) (Figure 3). Six patients had an increase in resting ejection fraction of ≥6 units

TABLE II Rest and Exercise Cardiovascular Effects of Metoprolol in Eight Patients

	Baseline	Metoprolol
Resting HR (beats/min)	87 ± 18	62 ± 9*
Peak exercise HR	133 ± 13	105 ± 30*
Resting systolic BP (mmHg)	128 ± 10	139 ± 15*
Peak exercise systolic BP	158 ± 26	170 ± 26
Resting LVEF	0.15 ± 0.06	0.25 ± 0.11*
Peak exercise LVEF	0.19 ± 0.11	0.28 ± 0.15
Peak VO_2 (ml/kg/min)	14.8 ± 3.0	16.1 ± 2.5*
Peak O_2 pulse (ml/beat)	9.0 ± 2.2	12.6 ± 1.8*

* $p < 0.05$ versus baseline.
Values are mean ± standard deviation.
BP = blood pressure; HR = heart rate; LVEF = left ventricular ejection fraction; VO_2 peak = peak exercise oxygen uptake.

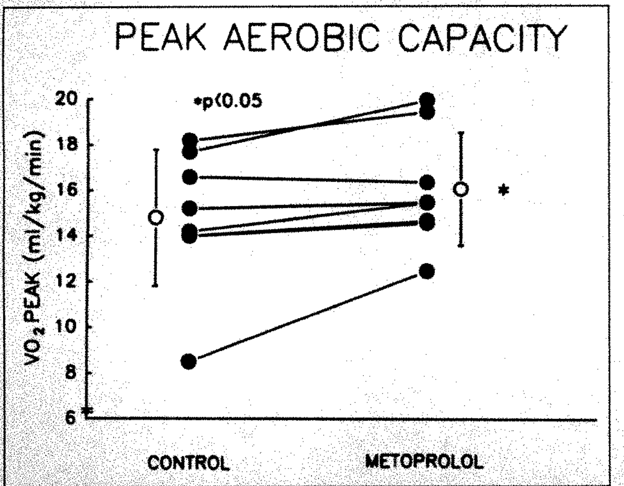

FIGURE 1. The peak exercise oxygen uptake (VO_2) increased from 14.8 ± 3.0 to 16.1 ± 2.5 ml/kg/min ($p < 0.02$).

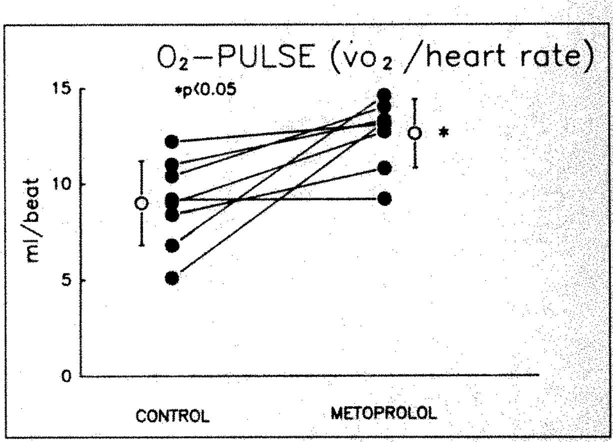

FIGURE 2. The mean oxygen (O_2) pulse at maximal exertion increased from 9.0 ± 2.2 to 12.6 ± 1.8 ml/beat ($p < 0.01$). VO_2 = peak exercise oxygen uptake.

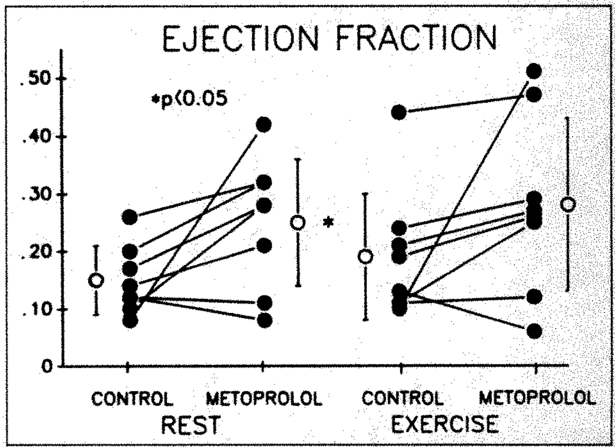

FIGURE 3. The mean resting ejection fraction increased from 0.15 ± 0.06 to 0.25 ± 0.11 ($p < 0.05$). Six of the 8 patients had an increase in the resting ejection fraction of ≥6 units. There was also a trend for the peak exercise ejection fraction to increase (0.19 ± 0.11 to 0.28 ± 0.15, difference not significant).

TABLE III Effects of Metoprolol on Circulating Plasma Catecholamines and Norepinephrine Appearance and Clearance Rates

	Baseline	Metoprolol
NE Rest (pg/ml)	613 ± 706	303 ± 142*
NE peak exercise (pg/ml)	1,715 ± 908	1,388 ± 404
EPI rest (pg/ml)	71 ± 50	40 ± 21*
EPI peak exercise (pg/ml)	134 ± 83	131 ± 44
NE appearance rate (μg/min/m^2)	0.40 ± 0.26	0.31 ± 0.12
NE clearance rate (liter/min/m^2)	0.85 ± 0.29	0.95 ± 0.18

* p <0.05 versus baseline.
Values are mean ± standard deviation.
EPI = arterialized venous epinephrine; NE = arterialized venous norepinephrine.

whereas 2 had no change. The change in ejection fraction remained borderline significant (p = 0.06) when the patient with the most dramatic response was excluded. The duration of supine exercise increased from 7.7 ± 3.0 to 9.1 ± 2.7 minutes (p <0.01). Despite the increase in exercise duration and work load, the peak exercise ejection fraction also tended to increase (0.19 ± 0.11 to 0.28 ± 0.15, p = 0.13).

Plasma catecholamines, norepinephrine kinetics and beta-adrenergic receptors: At baseline, mean resting arterialized venous plasma concentration of norepinephrine was elevated to 613 ± 706 pg/ml, and declined to 303 ± 142 pg/ml with metoprolol (p <0.05) (Figure 4). The change remained borderline significant (p = 0.06) when the patient with the most dramatic response was excluded. Resting norepinephrine decreased >100 pg/ml in 5 of the 8 subjects. The resting plasma concentration of epinephrine also declined (71 ± 50 to 40 ± 21 pg/ml, p <0.02) (Figure 5). During supine exercise, plasma norepinephrine and epinephrine increased substantially before and after metoprolol. Peak values at maximal exertion were not significantly affected by metoprolol (Table III).

Although the values did not achieve statistical significance, there was a trend for a decrease in the rate of norepinephrine appearance, from 0.40 ± 0.26 to 0.31 ± 0.12 μg/min/m^2 (p = 0.25) (Table III), associated with a small increase in the norepinephrine clearance rate (0.85 ± 0.29 to 0.95 ± 0.187 liters/min/m^2, p = 0.25).

There was no significant change in the β-adrenergic receptor number (1,334 ± 792 vs 1,344 ± 456 receptors/cell) or antagonist affinity (K_D) (72 ± 90 to 39 ± 32 picomolars) measured from circulating lymphocytes after metoprolol administration.

DISCUSSION

Ventricular function and exercise capacity: In this study, the 8 patients who tolerated metoprolol exhibited significant improvements in maximal exercise capacity during both supine and upright exercise. In addition, left ventricular function improved at rest and tended to increase at maximal exertion, despite the fact that a higher maximal work rate and a somewhat higher systolic pressure were achieved. Other studies have reported similar increases in ejection fraction after treatment with β blockers.[1,2,13] Although the prognostic implications of these findings are uncertain, the Veterans Administration Vasodilator Heart Failure Trial investigators noted that patients with CHF who experience an improvement in resting ejection fraction with vasodilators sustained the greatest overall improvement in survival.[14]

The significant improvement in VO_2 peak observed with metoprolol therapy indicates an increase in the maximal cardiac output. Because cardiac output is a function of heart rate and stroke volume, the reduction in maximal heart rate indicates that the maximal stroke volume increased, as demonstrated by the 40% increase in the oxygen pulse. Although normal subjects exhibit an increase in maximal stroke volume with β blockade,[15] such a finding is unexpected in patients with CHF. The trend toward an increase in exercise ejection fraction also supports this finding. Thus, cardiac reserve improved as evidenced by the increase in maximal exercise ejection fraction, the maximal oxygen pulse and the VO_2 peak. Engelmeier et al[2] also reported an improvement in exercise capacity and ejection fraction in patients with idiopathic cardiomyopathy treated with metoprolol, although VO_2 was not directly measured.

Catecholamine levels, norepinephrine kinetics and beta receptors: Circulating levels of norepinephrine represent an equilibrium of the rate of spillover from

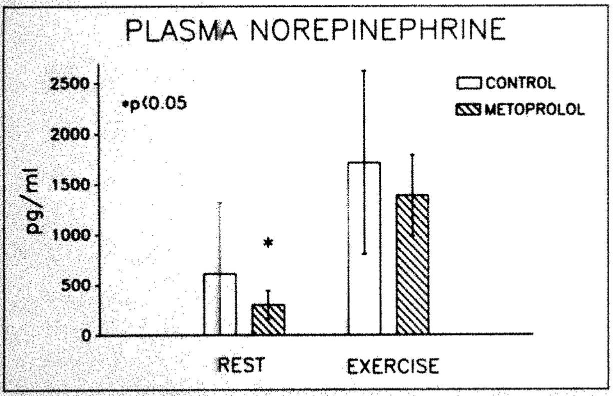

FIGURE 4. Resting plasma norepinephrine decreased from 613 ± 706 to 303 ± 142 pg/ml (p <0.05), whereas maximal exercise plasma norepinephrine levels were not significantly changed.

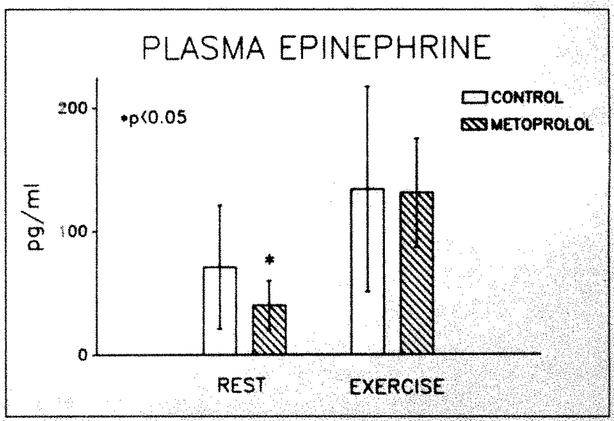

FIGURE 5. Resting plasma epinephrine was significantly reduced from 71 ± 50 to 40 ± 21 pg/ml (p <0.02), whereas maximal exercise epinephrine levels were unchanged.

sympathetic nerve terminals (appearance rate) and the rate of clearance from the circulation, which primarily occurs at the nerve varicosities. The spillover rate reflects total body sympathetic nervous system activity originating from both cardiac and noncardiac sympathetic nerves. The clearance rate is dependent on neuronal uptake of norepinephrine and on the cardiac output.[16] Acute and chronic administration of a variety of β blockers to normal subjects, patients with chronic hypertension or patients with acute myocardial infarction produces an increase in plasma norepinephrine.[17-19] The increased plasma norepinephrine is largely due to a reduction in clearance, which in turn is related to decreased cardiac output.[17,20]

In contrast, in the current study, chronic metoprolol therapy caused a decrease in circulating plasma catecholamines, a response that appears to be unique to patients with CHF. Neither the decrease in appearance rate nor increase in clearance rate of norepinephrine were statistically significant in the current study; however, the observed changes in kinetic rates are directly opposite those noted in the previously mentioned studies.[17,20] The reduced plasma norepinephrine is probably a reflection of a direct improvement in underlying cardiac function, with a resultant secondary reduction in sympathetic nervous system activity as has been reported to occur with the intracoronary infusion of dobutamine.[21] In contrast to metoprolol, vasodilators that only indirectly improve myocardial performance have little effect on plasma norepinephrine levels.[22] Moreover, the β blocker pindolol, which possesses intrinsic sympathomimetic activity, also does not alter plasma norepinephrine or improve myocardial function.[23]

Mechanisms of beta-blocking improvement: Beta-receptor up-regulation has been proposed to explain the beneficial effects produced by β blockers in some patients with CHF.[24,25] In contrast to our findings of no change in peripheral lymphocyte β-receptor numbers, Heilbrunn et al[13] reported an increase in myocardial β-receptor density with metoprolol that was associated with an increase in resting ejection fraction, stroke work index and contractile response to dobutamine infusion.

The bradycardiac effects of β blockers could also possibly be responsible for the observed beneficial responses. Prolonged tachycardia has been known to be a cause of reversible cardiomyopathy, although the mechanism remains elusive.[26] Slowing the heart rate produces an increased period of diastolic filling and myocardial perfusion which may improve myocardial energetics or diastolic function. Pindolol, which exhibits partial β-agonist activity and limited bradycardiac effects, does not appear to have beneficial effects in patients with CHF.[23] A recent report by Brown and Hudlicka[27] indicated that bradycardia pacing may actually prevent the development of a cardiomyopathy in rabbits exposed to large doses of norepinephrine.

Limitations: This study was not randomized or placebo controlled. However, it is unlikely that the observed changes reflect spontaneous improvement given the long duration of CHF and stability of symptoms before study entry. Moreover, both of the primary end points (ejection fraction and peak exercise VO_2) have been shown to vary little during placebo administration in patients with CHF.[28,29] Our trial further documented the stability of peak VO_2, which was similar on the familiarizing preentry test and baseline test performed at least 1 week later (14.2 ± 2.3 and 14.7 ± 2.9 ml/kg/min, difference not significant). Although 1 patient exhibited a dramatic response to metoprolol with a marked increase in ejection fraction and decrease in plasma norepinephrine, the overall changes in these measures remained borderline significant even when this patient was excluded from the analysis ($p = 0.06$ for both).

Despite these limitations, the current trial of metoprolol demonstrated an improvement in both resting ejection fraction and an increased maximal exercise capacity in patients with CHF. The improvements in cardiac function were associated with a decline in resting plasma norepinephrine and epinephrine but with no significant change in β-adrenergic receptor density on circulating lymphocytes.

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Digital Acoustical Analysis of Normal and Bimodal Björk-Shiley 60° Convexo-Concave Heart Valves

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Fracture of the outlet strut of the Björk-Shiley 60° convexo-concave (BS60CC) valve has been attributed to a bimodal closing pattern in certain valves in which the closing disk rotates about the inlet strut, causing upward displacement of the outlet strut and its eventual fracture. This article reports the in vivo studies of the normal BS60CC valve and the in vitro studies of the normal and bimodal BS60CC valves, using a digitial acoustical signal processing technique, in which the individual collisions (impact history) of the occluder disk with the components of the valve body are revealed during each closing cycle. In vitro analysis of the closing acoustical signals of normal BS60CC valves showed impact history cluster width (IHCW) means of 2.07 ± 0.85 ms (standard error), not significantly different from those of 1.86 ± 0.58 ms (standard error) observed in 38 clinically normal patients with BS60CC valves ($p > 0.1$). The bimodal valves showed IHCW of 6.14 ± 0.98 ms (standard error), in vitro, which was significantly greater than those observed in the normal in vitro valve group and in the normal patient population ($p < 0.0001$).

(Am J Cardiol 1990;66:849–854)

Fracture of the outlet strut and subsequent escape and embolization of the occluder disc has been reported for both aortic and mitral Björk-Shiley (Shiley Corporation) 60° convexo-concave (BS60CC) heart valve prostheses.[1–20] Such fracture is a catastrophic event requiring immediate diagnosis and valve replacement surgery. Approximately 64% of the 284 outlet strut fractures that have been reported to the US Food and Drug Administration (FDA) as of August 1989 have been fatal (*Device Experience Reports submitted by Shiley, Inc., to the Food and Drug Administration* [*FDA*]. *Quarterly updates of actuarial statistics regarding strut fracture in Björk-Shiley 60° convexo-concave valve prostheses, submitted by Shiley, Inc., to the FDA*). The BS60CC valve was available in the United States from 1979 to 1986 and exported from 1976 to 1986.[20] Shiley estimates that 81,791 BS60CC valves have been implanted in patients worldwide, since 1976 (*quarterly updates of actuarial statistics regarding strut fracture in Björk-Shiley 60° convexo-concave valve prostheses, submitted by Shiley, Inc., to the FDA*).

Between 1980 and 1984, in response to the outlet strut fracture problem, the valve manufacturer made numerous changes in the manufacturing and quality control procedures.[20] Based in part upon failure analysis of in vivo fractured valves[21–23] disk-opening forces were suspected as the cause of the outlet strut fracture and most of the earlier manufacturing changes focused on strengthening the weld of the outlet strut to the valve flange. While this may have resulted in an improved fatigue resistance of this union, it did not eliminate the strut fracture problem. Furthermore, strut fracture of the valve could not be duplicated with in vitro pulse duplicator studies even when extreme opening stresses were used.[20]

Subsequent observations of wear patterns on the occluder and outlet strut tip and contour profiling of the inlet strut of in vivo failed valves led to the conclusion by Shiley that extreme outlet strut stresses could occur during disc closure in certain valves exhibiting a "bimodal" disc closure pattern. In these valves, an improper contour match between the disc occluder and the adjacent surfaces of the inlet strut could result in multiple equilibrium points for the occluder in its closed position. The consequent rocking of the occluder on the inlet strut during closure could result in the occluder contacting the outlet strut at its tip, rather than at its base, as

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designed (see Figure 1). This contact at the tip of the outlet strut would apply excessive bending stresses to the weld union and could result in eventual fatigue failure. When out-of-tolerance valves were subjected to extreme closure stresses in a fatigue tester, fracture of the outlet strut was reported.[20]

In 1984, Shiley, Inc., implemented additional quality control procedures to assure proper contour match between the occluder and the inlet strut. There have been no reports of outlet strut fracture in the valves that have passed these additional quality control tests. However, production levels of the BS60CC valve were quite low after 1984 and the total clinical experience in patient years is limited.

There are currently no methods available for clinically screening patients with BS60CC heart valves that will identify those valves with a bimodal closure pattern. Although cinefluoroscopic techniques have identified fracture of the outflow strut and embolization of the occluder disc,[1-20] this technique has not and could not be expected to successfully identify any valves exhibiting bimodal closure. Since the hemodynamic characteristics of the bimodal valves do not differ from the normally closing valves before fracture, Doppler-echocardiography and echophonocardiography have not identified this abnormal valve group. This article reports the use of a digital acoustical signal processing system using the technique of deconvolution analysis (*Valve-Tracker II Digital Phonocardiograph, International Acoustics Incorporated. The mention of any commercial product in this report in no way should be construed as an endorsement for or discreditation of any such device by the FDA*) for in vivo and in vitro characterization of the closing motion dynamics of the BS60CC valve and for detection of the bimodal closing pattern in these valves.

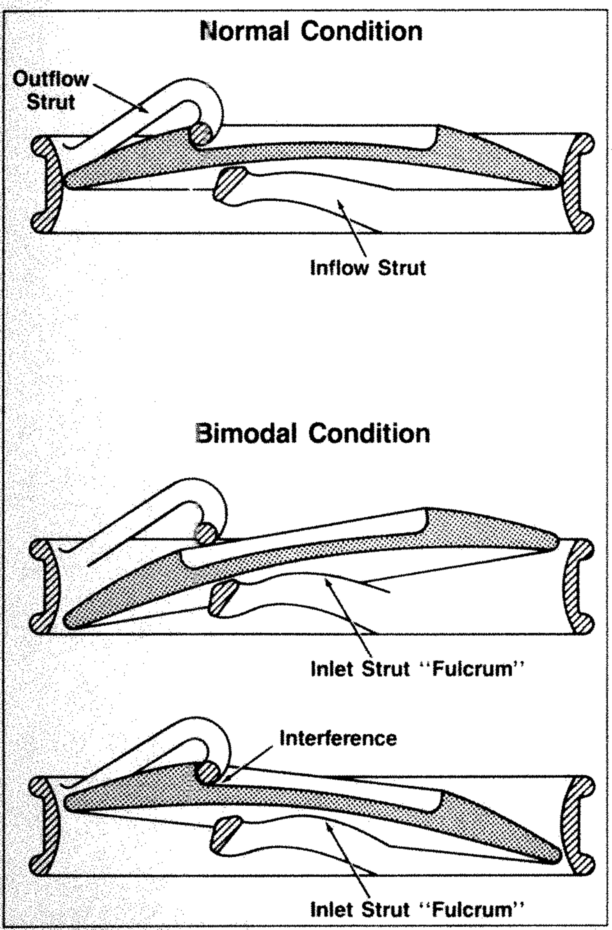

FIGURE 1. Schematic illustration of bimodal Bjork-Shiley 60° convexo-concave (BS60CC) valve (*lower illustration*), in which the occluder disc rotates about the inlet strut and contacts the tip of the outlet strut causing displacement and eventual fracture at its union with the valve flange. The closed position of the "normal" valve is shown in the *upper frame.*

METHODS

In vitro test valves: Two series of BS60CC, 29-mm, mitral valves were supplied to the FDA by Shiley, Inc. The "normal" series of valves ("A" valves) had passed all quality control tests that existed at the time the valve was withdrawn from the market in 1986, including those contour-matching procedures implemented in early 1984 to detect the bimodal closing pattern. The "bimodal" series of valves ("C" valves) had been specifically modified for the FDA by the manufacturer to exhibit the bimodal closure pattern. The "C" valves, when closed, displaced the outlet strut 1/1000th to 4/1000th inch.

Acoustical signal recording system: In vivo and in vitro valve acoustical signals were recorded with the digital phonocardiograph and accelerometer microphone. The accelerometer microphone frequency response (± 3 db) is 20 Hz to 10 KHz and its sensitivity is −60 db with reference to 1 volt/microbar. The amplifier bandpass (−3 db) is 20 Hz to 2.7 KHz with anti-aliasing filters (−30 db) at 4 KHz. The analog-to-digital conversion rate was 8,000 points per second with 12-bit accuracy. All digitized records were stored on diskette for evaluation with the system's digital deconvolution analysis technique.

Clinical recordings: The clinical population consisted of both male and female patients with BS60CC single aortic (20 patients), single mitral (13 patients) and double (3 patients) valve replacements, dating from 1979 through 1986. The digital phonocardiogram recordings were obtained during routine clinical visits and each of these patients was considered to have normally functioning valve prostheses based upon routine clinical evaluations. The accelerometer microphone, mounted in its acoustically matched assembly, was secured with denture adhesive at the chest location of greatest prosthetic valve sound intensity, usually at the mid left sternal border for aortic valve prostheses, and at the lower left sternal border for mitral prostheses. Auscultatory signals were recorded during breath holding at end-expiration, with the patient supine and the head elevated approximately 15°.

Pulse duplicator recordings: The test valves supplied by Shiley, Inc., were mounted in a left-sided heart duplicator (Figure 2) developed at the FDA Center for Devices and Radiological Health.[28] The duplicator used a variable speed piston pump with flywheel and brake, an eccentric cam follower drive and a low friction rubber collar piston within a lucite left ventricular chamber to minimize vibrational noise and cycle-to-cycle pressure variability. Thin walled latex gooch tubing with clamps distributed along its length simulated systemic vasoelasticity to allow a "physiologic" pressure profile to be produced.

The valves were mounted, with uniform orientation, in the mitral position of the left-sided heart duplicator, with the accelerometer transducer attached to the outer structure of the duplicator just upstream of the valve, over the "atrial" chamber. A bioprosthetic heart valve was mounted in the aortic position of the duplicator. Stroke rate was 70 beats/min, systolic/diastolic pressures were 120/80 mm Hg and systole was 40% of the total heart cycle. Multiple recordings were made of the acoustical signals of each of the test valves and stored on diskette. The recordings were blinded and submitted for signal analysis.

Mechanical measurements and tests: Measurements were made of the force applied to the outlet strut by the closing occluder disc, in the left-sided heart duplicator, under a range of pressures, rates and cardiac outputs by means of strain gage transducers affixed to the outlet strut. Durability tests were performed in an accelerated tester, using a glycerol and water mixture comparable to the viscosity and density of blood, at a rate of 1,100 to 1,200 cycles/min with peak systolic pressures between 120 and 140 mm Hg.

Data analysis: The acoustical signals produced by the closing prosthetic mechanical valves, in vivo and in vitro, were analyzed by a specialized set of the signal processing technique sometimes referred to as deconvolution analysis, detailed in Appendix 1. The use of this technique for studying asynchronous closure of mechanical bi-leaflet valves has been reported earlier.[24,25]

This technique reveals the impact history of the acoustical signal, that is, the pattern of collisions that were responsible for creating the acoustical signal. For the BS60CC valve, the pattern of collisions of the disc with the valve's flange and inlet and outlet struts is

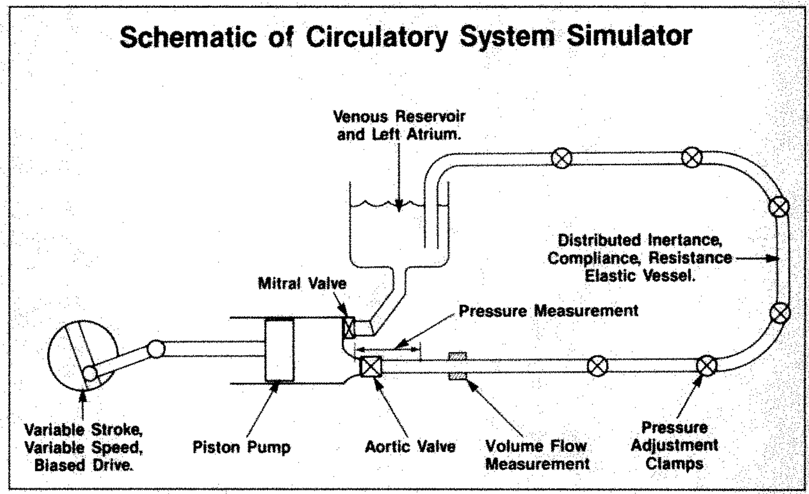
Schematic of Circulatory System Simulator
Venous Reservoir and Left Atrium.
Distributed Inertance, Compliance, Resistance Elastic Vessel.
Mitral Valve
Pressure Measurement
Variable Stroke, Variable Speed, Biased Drive.
Piston Pump
Aortic Valve
Volume Flow Measurement
Pressure Adjustment Clamps

FIGURE 2. Schematic illustration of circulatory system simulator. The test valve was mounted in the mitral position with accelerometer microphone cemented upstream of the valve.

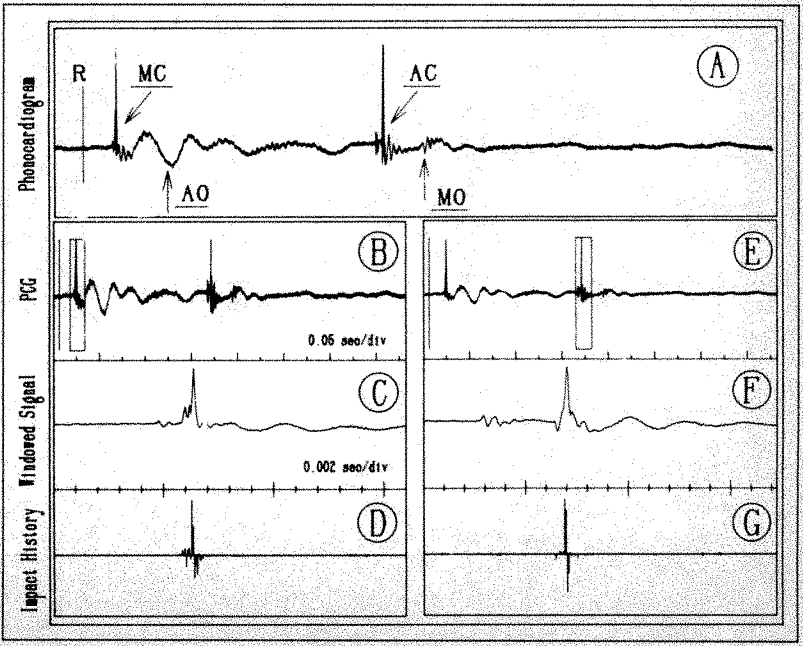

FIGURE 3. Digital phonocardiogram "PCG" (*A*) of a patient with a Bjork-Shiley 60° convexo-concave (BS60CC) mitral and aortic valve replacement shows the high frequency mitral (MC) and aortic (AC) valve closing signals. Deconvolution analysis of the mitral (*D*) and aortic (*G*) valve closing signal shows impact history cluster widths of approximately 2 ms. MO = mitral open; AO = aortic open.

characterized by the geometry of the impact history clusters and, in this study, principally by their duration. Impact history cluster duration was measured in each of the recorded cardiac cycles or left heart duplicator cycles as that duration which included 90% (computer measured) of the energy of the cluster.

Statistical analysis: The general linear models (GLM) procedure of the SAS (SAS Institute, Inc.) software system for data analysis was used to perform analysis of variance (ANOVA).

RESULTS

Figure 3 shows the analysis of a single cardiac cycle of a clinically normal patient with a BS60CC mitral and aortic valve replacement, in 1984. The upper frame of the report (A) is the recorded digital phonocardiogram (time scale = 0.05 sec/div), with the position of the R-wave indicated by the single vertical bar. The digital phonocardiogram of all mitral and aortic BS60CC valves, in vivo, showed typically narrow, high-frequency prosthetic valve closing signals (MC and AC), most often comprised of a single, intense acoustical signal which is often preceded by 2 to 10 ms by a low intensity, lower frequency acoustical signal (seen best in Figure 3, C and F). Such acoustical signal patterns for the Björk-Shiley valve have been reported earlier,[26] with echocardiographic evidence of the first low intensity signal occurring with the start of the disc closure and the second intense signal occurring with final closure of the disc.

The windowed mitral (B) and aortic (E) valve closing acoustical signals are expanded and shown in frames C and F, respectively. Frames D and G are the impact history patterns of each of the closing valve signals (time scale = 0.002 sec/div) and reveal the typically narrow, singular impact history clusters that describe the collision of the occluder disc with the surfaces of the valve flange and finally with the surfaces of the inlet strut.

Figure 4 shows the distribution of impact history cluster widths in 172 cardiac cycles of 39 valves in the 36 clinically normal patients studied. The mean impact

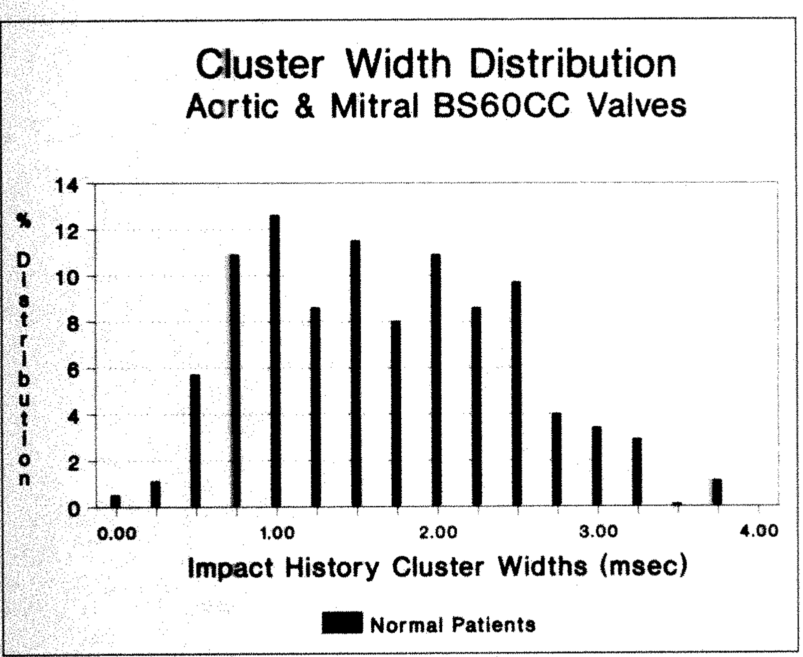

FIGURE 4. Distribution of impact history cluster width durations in clinically normal patients with Björk-Shiley 60° convexo-concave (BS60CC) valves.

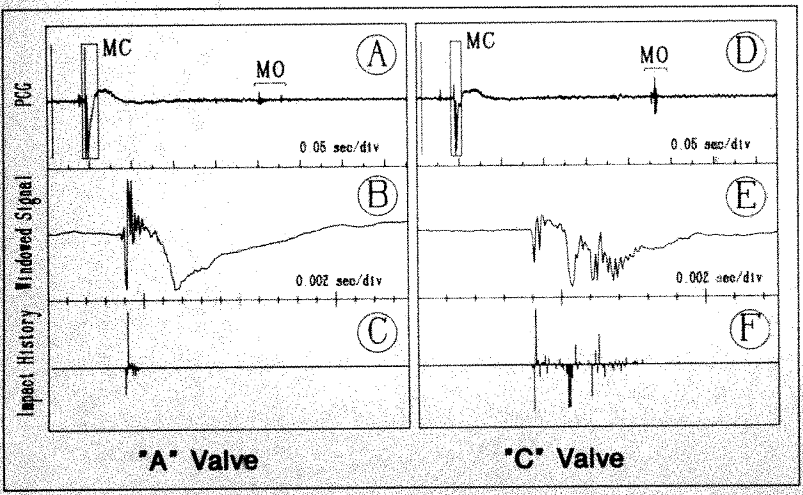

FIGURE 5. Deconvolution analysis of "normal" Bjork-Shiley 60° convexo-concave (BS60CC) valve (*C*) in left-sided heart duplicator shows an impact history cluster width duration of approximately 2 ms. Deconvolution analysis of closing signal of "bimodal" BS60CC valve (*F*) shows an impact history cluster width duration of approximately 7.5 ms.

history cluster width duration was 1.86 ms ± 0.58 ms (standard error) with a range of 0.12 to 3.75 ms. There was no significant difference between the impact history cluster width duration means in aortic or mitral valve replacements (p >0.1).

Figure 5 shows the acoustical signal recordings and deconvolution analysis of a "normal" ("A") and bimodal ("C") BS60CC valve cycled in the left heart duplicator. The valve closing signals are preceded by approximately 12 to 20 ms by a lower intensity, lower frequency acoustical signal. Unlike the typical in vivo recordings, the valve opening signals are clearly seen. The impact history clusters seen in the 90 left-sided heart duplicator cycles of 20 BS60CC "A" valves are narrow and singular in appearance (frame C), similar to those seen in the clinical patient population. The mean impact history cluster width of these valves was 2.07 ± 0.85 ms (standard error) with a range of 0.38 to 4.88 ms.

The impact history clusters seen in the 82 left-sided heart duplicator cycles of 15 bimodal ("C") valves are significantly broader (frame F) than those seen with the normal valve in the left-sided heart duplicator or in the clinical groups. The mean cluster width duration in the bimodal valve group was 6.14 ± 0.98 ms (standard error) with a range of 4.0 to 9.76 ms.

Figure 6 shows the impact history cluster width distribution in the patient groups, and in the left heart duplicator study of the normal and bimodal valves. There was no significant difference between the impact history cluster width duration means in the patient population with single valves and the normal "A" valve left-sided heart duplicator study (p >0.1). The impact history cluster width duration distribution of the bimodal "C" valves showed a significantly higher mean (p <0.0001) than any other group. However, the impact history cluster width duration distribution of the normal "A" valves showed a significantly higher mean (p <0.01) than the patient population with double valves.

Measurement of the force applied to the outlet strut by the occluder disc in the left-sided heart duplicator, under a range of pressures, rates and stroke volumes, showed relatively low force of 1.1 to 4.5 newtons in the normal "A" valves, and significantly higher forces of 9.8 to 18.7 newtons in the bimodal "C" valves. Lifetime calculations based upon these measurements predict no fatigue failure of the normal valves, but predict failure in the bimodal valves between 1 and 700 days. Durability tests in an accelerated tester at 1,100 to 1,200 cycles/min, at pressures of 120 to 140 mm Hg, did not produce failure in either the normal or bimodal valves in the equivalent of 420 days.

DISCUSSION

Although it has been reported that the excessive forces on the outlet strut generated during closure of the bimodal valve may be responsible for fracture of the outlet strut, such fracture has been shown in vitro only in markedly bimodal valves with extreme closure stresses.[20] While the significantly higher than normal forces on the outlet strut of the closing bimodal valve, found in this study, predict fatigue failure of the strut between 1 and 700 days, such fatigue failure was not observed in an accelerated tester in the equivalent of 420 days. Thus, this postulated mode of outlet strut fracture requires further verification.

The broad impact history cluster width of the bimodal BS60CC valve characterizes the closing motion of the occluder disc as it rotates about the inlet strut and torques the outlet strut, causing repeated impacts of the disc on the metal structures of the valve ring. This broad impact history pattern differentiates this bimodal valve from the normally closing valve in vivo and in vitro and may present a methodology for identifying a subset of patients with the bimodal BS60CC valves.

Because the risk of outlet strut fracture in the BS60CC valve is significantly lower than the surgical

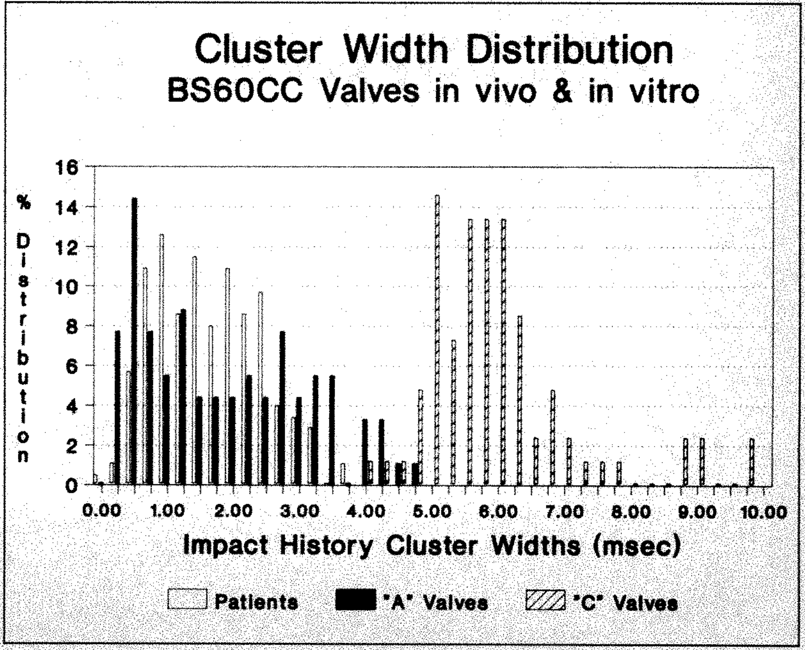

FIGURE 6. Impact history cluster width durations in patient population (*open bars*) and in left-sided heart duplicator study of "normal" valves (*solid bars*) and "bimodal" valves (*striped bars*).

risk of elective explanation of these valves, such a procedure has not been recommended.[20,27] However, identification of a subset of patients with high risk of valve fracture could markedly change these relative risk factors.

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APPENDIX

The observed acoustical signal is modeled as the output of a recursive, linear filter. This filter represents the acoustical response of the entire valve cage, which is being impacted by a disk or other occluding object, and is assumed to have a stable impulse response. The time taken for the response to decay to one-half the original value is called the "mean decay time" (τ_d) of the filter.

This filter is assumed to be excited by an impulse input, which represents the discrete impacts of the occluding element against the valve cage. The autocorrelation of this input can be shown to be impulsive as well, with a peak at $t = 0$ and the next peak at the "correlation time" (τ_c) of the input.

When the condition $\tau_c > \tau_d$ holds, both the filter parameter and the corresponding input signal can be separately estimated.

Specifically, since the filter is purely recursive, it has a Z transform which can be written as the following:

$$A(z) = \frac{1}{\sum_{p=0}^{N} a_p z^{-p}} \qquad a_0 = 1$$

where the a_p are the filter parameters to be estimated, and N is the order of the filter. In the present application, an order of 10 and 12 has been found to be sufficient.

Then, with the autocorrelation of the input signal x(n) estimated as $R_p = \Sigma_n X(n)\, X(n+p)$ the filter parameters are computed as the solution to the system of linear equations:

$$\sum_{p=1}^{n} a_p R_{q-p} = -R_q \quad q = 1 \ldots N$$

With the filter parameters computed, the impulsive input signal can be estimated as the following:

$$I(n) = \sum_{p=0}^{N} a_p X(n-p)$$

The significance of the pulses in this signal can be derived from an appreciation of the mechanics of the occluding element of the valve and the timing of the pulses relative to the observed signal. In particular, discrete peaks in the impulse signal correspond to discontinuities in the original acoustic signal. These discontinuities in turn locate the times of impulsive external forces.

"Cardioprotection" — Not All Calcium Antagonists Are Created Equal

Franz H. Messerli, MD

The term "cardioprotection" ("Myokardschutz")* was coined by Fleckenstein[1] more than 2 decades ago to describe the salutatory effects of calcium antagonists on isoproterenol-induced myocardial necrosis. A few years later Nayler et al,[2] by using verapamil, succeeded in protecting the heart muscle from ischemic injury, an effect that was subsequently documented for other calcium antagonists as well.[3,4] These early experimental studies were extended by a variety of clinical and experimental findings attesting to the cardioprotective effect of calcium antagonists. Thus, calcium antagonists were reported to: (1) improve coronary flow; (2) reduce afterload; (3) suppress ventricular arrhythmias; (4) diminish myocardial cell damage by preventing intracellular calcium overload during episodes of ischemia; (5) diminish platelet aggregation in contrast to β blockers; (6) exert antiatheromatous effects in some animal models; and (7) reduce left ventricular hypertrophy and enhance left ventricular filling not only by improving the active relaxation process but also distensibility—these latter effects seem to be most pronounced in patients with arterial hypertension and can be expected to translate into a therapeutic benefit only after sustained therapy.

These promising experimental reports seemed to attest to the attractiveness of calcium antagonists in the treatment of myocardial infarction and coronary artery disease. Recent angiographic studies with verapamil[5] and nifedipine,[6] documenting a beneficial effect on coronary stenoses, support the animal data (although they showed no decrease in mortality). However, the attractiveness of calcium antagonists was decidedly put into question less than a year ago by Held et al,[7] who systematically reviewed 28 randomized trials, creating a data base of more than 19,000 patients. They came to the conclusion that "calcium antagonists do not reduce the risk of initial or recurrent infarction or death when given routinely to patients with acute myocardial infarction," and therefore they discouraged the prophylactic use of calcium antagonists during or after acute myocardial infarction.

This review was extensively commented on in the lay press, and *The Wall Street Journal*[8] discussed it under the heading "Calcium Channel Blockers Called Ineffective Against Heart Disease." The disheartening findings and recommendations flew in the face of most of our colleague cardiologists who routinely had been using calcium antagonists in more than 40% of patients after uncomplicated myocardial infarction.[9] Held et al[7] nevertheless indicated that there was a slight trend toward fewer reinfarctions in patients treated with verapamil and diltiazem (although there was no effect on mortality) and that therefore the data were consistent with the possibility that calcium antagonists that reduced heart rate might reduce the risk of reinfarction. They candidly suggested that this hypothesis "should therefore be interpreted with caution and specifically examined in further trials."

This is exactly what Fischer Hanson and co-workers[10] did in a carefully designed double-blinded, randomized, placebo-controlled, multicenter trial assessing the "cardioprotective" effects of verapamil after acute myocardial infarction, The Danish Verapamil Infarction Trial (DAVIT II).[10] Their previous study, the DAVIT I,[11] failed to show a significant reduction of overall mortality or reinfarction rate after 6 months of verapamil treatment. A retrospective subanalysis, however, demonstrated a highly significant reduction in mortality only in the subset of patients who received verapamil from day 2 to day 180. Encouraged by this subanalysis, the investigators embarked on a new study, the DAVIT II, in which treatment was started between day 7 and day 15 after the acute myocardial infarction. As can be seen elsewhere in this issue, DAVIT II documented a significant reduction in the reinfarction rate in the verapamil group when compared with the placebo group, although the difference in the overall mortality rates failed to reach statistical significance. However, by combining data from DAVIT I with DAVIT II, creating a data base of more than 3,100 patients, a reduction of about 25% in major events and deaths was documented in verapamil-treated patients when compared with results in those taking placebo.

The results of DAVIT II are provocative, but leave several important questions unanswered: Since "cardioprotection" was documented only when verapamil therapy was begun 1 week after the acute myocardial infarction, how should patients be protected during these first days of the postinfarction period? What are the clinical criteria that allow the practicing physician to decide whether a patient is a candidate for verapamil or

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*Unfortunately, "cardioprotection" has become a wastebasket term for all kinds of beneficial effects that drug therapy may exert on the heart, ranging from suppression of ventricular ectopy to a decrease in cardiac death rate.

a β blocker? Should verapamil and a β blocker be combined in certain patients and, if so, can the effect of the two drugs on reinfarction rate be expected to be additive? Is this cardioprotective effect specific to verapamil or can it be considered as a class effect—provided that the calcium antagonist is given 1 week after the acute myocardial infarction?

What then are the conclusions that we can draw from the DAVIT II data and how do they fit into the realm of the review by Held and collaborators? Calcium antagonists are a heterogeneous group of drugs. Conceivably, cardioprotective properties (decrease in the reinfarction rate and/or mortality) may vary from one agent to the other and reach clinical significance only in those calcium antagonists that diminish heart rate, as Held et al suggested. Conversely, some calcium antagonists, by producing profound reflexive cardioacceleration, may increase myocardial oxygen requirements and thereby paradoxically increase the risk of myocardial infarction in susceptible patients. Of note, calcium antagonists may also adversely affect prognosis when given during myocardial infarction or very early in the postinfarction period because, in this situation in patients who have a total occlusion, they may merely produce a negative inotropic effect. It seems, therefore, that patients with a noncomplete occlusion and/or good collateral circulation and no symptoms and signs of congestive heart failure are the best candidates for cardioprotective treatment with verapamil. This view is supported and extended by data from the Multicenter Diltiazem Postinfarction Trial Research Group documenting diltiazem to exert a clinical benefit only in patients without pulmonary congestion[12] and in those with non-Q-wave infarction.[13] Preliminary data indicate that the reduction in reinfarction rate was more pronounced in patients with a history of hypertension.[14]

Does the DAVIT II study annihilate the conclusions of the thorough review of Held et al, demonstrating no effects of calcium antagonists after myocardial infarction? Certainly not. However, it should replace therapeutic nihilism (i.e., all calcium antagonists are useless in patients with myocardial infarction) by cautious optimism (i.e., certain calcium antagonists, such as verapamil, are beneficial in selected patients in the postinfarction period, significantly reduce reinfarction rates, and may prolong life).

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Percutaneous Transluminal Coronary Angioplasty in Octogenarians With Unstable Coronary Syndromes

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and Earl Beard, MD

Coronary artery disease is a common and crippling condition in the elderly population. It is estimated that limitation of activity and compromised quality of life occurs in 85% of men and 55% of women in older age groups (>75 years) who have cardiovascular disease.[1] Little information has been reported regarding the outcome of percutaneous transluminal coronary angioplasty (PTCA) in octogenarians with unstable coronary syndromes. This is because older patients are usually excluded from randomized trials for interventional treatment, and today such treatment modalities are usually avoided unless they prolong longevity. This report documents our experience with PTCA in a group of elderly patients with unstable coronary syndromes. For this study, a special computerized data base was formulated from retrospective reviews of medical records, cineangiograms and patient interviews.

From July 1987 through June 1989, 53 elderly patients (mean age, 83 years; range 80 to 89) underwent PTCA for unstable coronary syndromes (Figure 1) that included angina at rest, progressive angina and early postinfarction angina. There were 31 men and 22 women in the study. Significant multivessel disease was observed in 38 patients. Thirteen patients (25%) had previously undergone coronary artery bypass surgery (mean interval, 13 years) and 14 (26%) had experienced previous myocardial infarction. In the overall group, mean left ventricular ejection fraction was 45% (range 20 to 60%). The electrocardiogram was normal in only 10 patients. Ischemic ST- and T-wave changes were observed in 23 patients during pain.

Before undergoing PTCA, all patients received ≥2 antianginal medications, including oral nitrates, β-adrenergic or calcium channel blockers; 21 patients were given nitroglycerin intravenously. Aspirin was given when not contraindicated. Informed consent was given in all cases. All procedures were performed using standard steerable guidewires and dilation catheters.

PTCA was attempted in the most significant (culprit) lesions: 1-vessel PTCA was performed in 39 patients, 2-vessel PTCA in 12 and 3-vessel PTCA in 2. The procedure was considered successful if stenosis was reduced to <50% of lumen diameter with clinical improvement in symptoms and no major complications.

Results of all procedures are shown in Figure 2. Primary success was achieved in 44 patients (83%). In unsuccessful procedures, complications consisted of acute myocardial infarction in 3 patients (5.5%), emergency coronary artery bypass surgery in 4 (7.5%) and death in 1 (1.8%). PTCA was unsuccessful in 1 patient who remained symptomatic on medical therapy. Noncardiac complications occurred in 10 patients and included hematoma (4), pseudoaneurysm (1), renal insufficiency (4, with 2 requiring dialysis) and sepsis (1). The mean hospital stay was 4 days for patients undergoing successful procedures and 13 days for those in whom PTCA was initially unsuccessful.

Follow-up data were available for 40 of 44 patients (91%) in whom PTCA was initially successful (Table I). Four patients were not from the United States, and we were unable to obtain follow-up data from them. For a

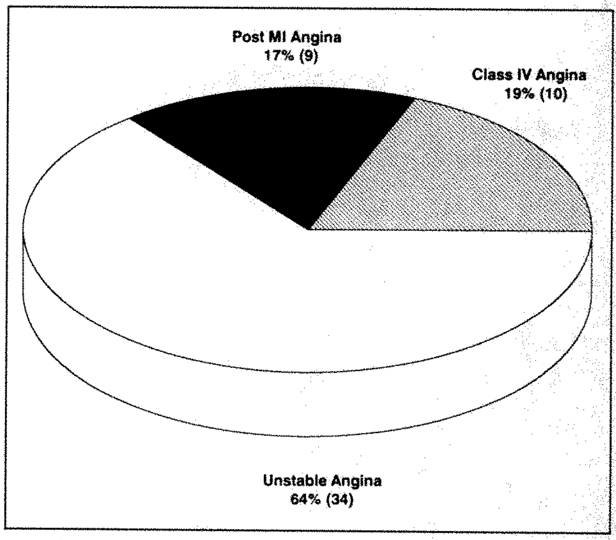

FIGURE 1. Clinical presentation of 53 elderly patients who underwent percutaneous transluminal coronary angioplasty procedures. MI = myocardial infarction.

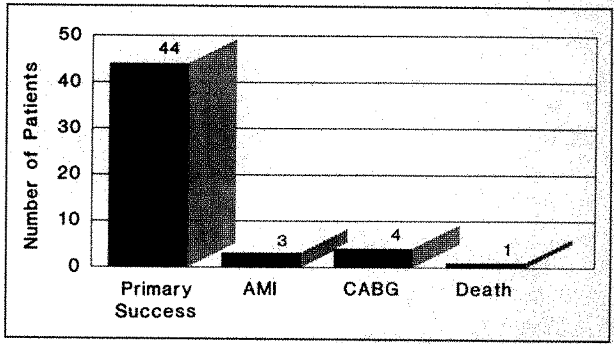

FIGURE 2. Initial results of percutaneous transluminal coronary angioplasty procedures. One patient (not shown here) remained symptomatic on medical therapy. AMI = acute myocardial infarction; CABG = coronary artery bypass graft.

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TABLE I Follow-Up Summary of 40 Patients with Successful PTCA

Interval (mo.)	Incident (no. of cases)			
	Repeat PTCA	MI	CABG	Death
0–12	9	1	2	2
13–24	3	0	1	1
>24	2	0	1	1
Total	14	1	4	4

CABG = coronary artery bypass graft procedures; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

mean duration of 14 months (range 6 to 34), 87% of patients who underwent primary or repeat PTCA, or both, continued to show clinical improvement and have event-free survival in the first year. During the subsequent 2 years, 75% of patients had sustained improvement without a major coronary event.

Published reports are devoid of controlled studies comparing the effectiveness, advantages and complication rates of PTCA over medical therapy in octogenarians. The risks that preclude PTCA when medical treatment has failed should be addressed by randomized studies. Our results are consistent with those from nonrandomized studies[2,3] in a comparable group of patients in whom procedural success rates of 67 to 80% were achieved, with a 6 to 14% incidence of emergency coronary bypass surgery and a 0 to 19% mortality. Our study is also consistent with other reports of elderly patients undergoing PTCA who have demonstrated lower success rates, shorter durations of sustained relief from symptoms, and higher morbidity and mortality rates than those reported in younger patients with similar syndromes.[4,5] This is likely due to the diffuse nature of disease and lesion complexity seen in elderly patients.

For our patients, successful PTCA (after failure of intensive medical treatment) resulted in medical stabilization, early hospital discharge and improvement in activity levels. Thus, despite the significant morbidity associated with this type of interventional procedure, the limited information available on PTCA for older patients with unstable coronary syndromes suggests that PTCA is a reasonable therapeutic option for palliation of symptoms and improvement in quality of life.

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Frequency and Causes of Failure with Contemporary Balloon Coronary Angioplasty and Implications for New Technologies

Joel K. Kahn, MD, and Geoffrey O. Hartzler, MD

Over the past decade of percutaneous transluminal coronary angioplasty (PTCA), greater operator experience and improvements in balloon catheters and guidewires have resulted in lesion success rates of ≥90%.[1,2] Despite the improved success of contemporary PTCA, numerous new technologies, including lasers, stents and atherectomy devices, have recently been introduced and championed as potential alternatives to the balloon catheter. The ease and success of current balloon procedures mandate that new therapies must either increase the primary success rates of interventional approaches, eliminate or help manage complications, or reduce restenosis. To better appreciate deficiencies with contemporary PTCA techniques that may be addressed with non-balloon catheter technologies, we analyzed the frequency, cause and outcome of failed PTCA in our most recent experience.

Patients undergoing PTCA during the calendar year 1989 for indications other than acute myocardial infarction were selected for analysis. Angiographic success or failure for each lesion attempted was coded prospectively in a computer data base. Successful angiographic dilatation of a lesion was defined as a reduction in diameter stenosis after PTCA to ≤40% in multiple views. Clinical and procedural records were reviewed in detail for all PTCAs with ≥1 unsuccessful dilatations. Multivessel PTCA was considered present when lesions in ≥2 epicardial coronary arteries or their major branches were dilated.

A total of 1,286 PTCAs were performed for indications other than acute myocardial infarction. A total of 3,398 lesions were attempted (2.6/procedure, range 1 to 14). Angiographic success was achieved in 3,272

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TABLE I Mode of Failure of Balloon Coronary Angioplasty in 126 of 3,398 Narrowings Electively Attempted in 1989

	No. (%)
Failure to cross lesion	86 (2.5)
Failure to cross with guidewire	
Chronic total occlusion	45 (1.3)
Severe tortuosity	18 (0.6)
Retrograde dilatation	4 (0.1)
Complex lesion preventing wire	6 (0.2)
Failure to cross with balloon catheter	
Severe tortuosity	9 (0.2)
Retrograde dilatation	4 (0.1)
Failure to dilate	37 (1.1)
Rigid artery at narrowing	20 (0.6)
Severe dissection	17 (0.5)
Emboli to distal artery	3 (0.1)

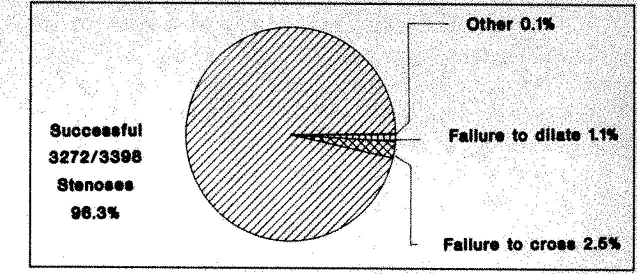

FIGURE 1. Angiographic results of 1,286 elective percutaneous transluminal coronary angioplasty procedures performed during 1989. Success was defined as reduction of luminal diameter narrowing to ≤40%.

(96.3%). A failed attempt at dilating a lesion occurred in 126 lesions in 122 patients. In 29 patients the failed stenosis was the only 1 attempted during the procedure, and in 93 patients successful angioplasty was accomplished in certain areas in addition to failure at ≥1 stenoses.

The reasons for failed PTCA are shown in Figure 1 and listed in Table I. The most comon reason that PTCA was unsuccessful was an inability to cross a lesion with either a guidewire or a balloon catheter, which occurred in 2.5% of all lesions attempted. This was due to the presence of chronic total occlusions, to severe tortuosity of the coronary vasculature, often combined with aortofemoral tortuosity, to attempted dilatations of native vessels through saphenous vein grafts in a retrograde direction, as previously described,[3] or to complex lesion characteristics that prevented wire passage. An additional 1.1% of attempted lesions could not be dilated. In some patients, excessive lesion rigidity prevented full balloon expansion, despite high inflation pressures and often to the point of multiple balloon ruptures. In 17 other patients, a severe arterial dissection resulted in luminal compromise. Finally, clinically significant emboli of friable vein graft material in 2 procedures and of embolized thrombus in 1 procedure resulted in absent anterograde coronary flow, and were considered failed procedures.

This study provides a perspective on the status of PTCA after a decade of development. Advances in balloon and guidewire production now permit successful PTCA in >96% of lesions in a broad spectrum of patients. The available low-profile balloon catheters with enhanced guidewire steerability routinely permit successful dilatations of lesions in distal and tortuous segments of native coronary arteries, saphenous vein grafts and internal mammary arteries. In contrast, most current multifiber laser catheters and atherectomy devices have high profiles and relatively inflexible shafts that currently limit their application to predominantly large proximal vessels without significant tortuosity.

It would seem more appropriate to use these newer technologies as specialty items for particular anatomic indications. One example that highlights some of the weaknesses of conventional PTCA techniques is the recanalization of chronic total occlusions. With appropriate selection and technique, approximately 75% of the chronic occlusions attempted can be treated successfully.[4] Our failures with chronic total occlusions resulted from an inability to cross the occlusion with a guidewire. Unfortunately, all the coronary excimer laser systems and coronary atherectomy devices now under investigation require guidewire support for safe coaxial advancement. Therefore, these technologies are not anticipated to have a significant impact on success rates for chronic total occlusions in the near future. Similarly, severe tortuosity was the second most common reason for failed PTCA. As noted above, it is unlikely that any of the non-balloon devices will be superior to balloon catheters in negotiating these segments. More optimistically, rigid lesions that would not dilate despite high inflation pressures, accounting for 0.6% of all lesions attempted, might yield to new devices. Based on early experiences, these lesions might be expected to respond to high-speed, rotational, ablative catheters and possibly to catheter-based lasers.

In addition to enhancing primary success rates, new devices may win a role in the catheterization laboratory if they can assist in the management of complications of PTCA. The 2 modes of failed PTCA resulting in complications in this study were severe arterial dissections and embolism to distal vessels, together occurring in 0.6% of lesions attempted. The management of arterial dissection has been assisted by the development of autoperfusion balloon catheters, permitting prolonged inflations during attempts to tack back intimal flaps while permitting anterograde flow.[5] Very early experiences indicate that new devices may further assist in the approach to severe dissections, including the placement of balloon-expandable stents and the sealing of dissections with laser-heated balloons.

The final rationale for shifting to greater use of new interventional devices would be the demonstration of reduction in restenosis after PTCA. To date there is insufficient data available to indicate that any of the newer systems effect the intimal hyperplastic response to arterial manipulation.

PTCA has matured to an extremely effective technique. Furthermore, continued improvements in conventional balloon catheter and guidewire technology can be expected to result in even higher success rates. This analysis of modes of failed PTCA procedures indicates that the newer non-balloon devices under investigation, currently limited by higher profiles, over-the-wire guidance, and inflexibility, may be expected to have a relatively minor impact on the overall success rate of contemporary PTCA. However, as all of the new technologies have been introduced only in the last 2 years, further improvements in their performance can be anticipated and will require ongoing comparisons with PTCA.

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Usefulness of Plasma Phospholipid N-3 Fatty Acid Levels in Predicting Dietary Fish Intake in Patients with Coronary Artery Disease

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An association between decreased cardiovascular mortality and high dietary fish intake[1-5] has suggested a possible protective role for n-3 fatty acids against the development of coronary artery disease (CAD). An inverse relation has also been observed between the risk of CAD and eicosapentaenoic acid (EPA) levels in various tissues.[6-10] A reasonable but unproven assumption is that tissue levels of n-3 fatty acids correlate with dietary fish intake. To test this assumption, we investigated whether a relation exists between quantity of chronic fish consumption and levels of n-3 fatty acids in plasma phospholipids, using a previously validated food frequency questionnaire.[11] Plasma phospholipids were chosen because they are the plasma lipids least sensitive to changes in short-term dietary fat intake.[12,13] Patients with established CAD were chosen because they are the group in which n-3 fatty acid levels have been most intensively studied.

Thirty-six patients aged 35 to 70 years with angiographically documented CAD were studied before their enrollment in a larger trial of patients receiving fish oil supplements. No patients were receiving supplements before enrollment. All patients completed a dietary food frequency questionnaire developed by the Nurses Health Study group at Harvard Medical School.[11] The questionnaire divides fish into three categories: "canned tunafish (3–4 oz)", "dark meat fish, e.g., mackerel, salmon, sardines, bluefish, swordfish (3–5 oz)" or "other fish (3–5 oz)". Questionnaires were scored for fish intake, and daily dietary n-3 fatty acid intake was calculated according to standard tables for average n-3 fatty acid content in fish.[14] All patients were fasting when plasma samples were obtained.

Total lipid extractions were performed on all plasma samples using a 3:2 hexane/isopropanol mixture (with a 20:1 solvent/plasma ratio) and washed with 6% sodium sulfate.[15] The plasma phospholipid fraction was separated from total lipid by thin-layer chromatography using an 83.3% petroleum ether/14.7% ethyl ether/1.9% glacial acetic acid solvent mixture.[16] Each phospholipid sample was then esterified in the presence of methanolic HCl[17] and analyzed by gas-liquid chromatography (Hewlett-Packard Model 5980) under the following conditions: column, 0.32 mm × 100 m, phase, 90% biscyanopropyl, 10% phenylcyanopropyl siloxane (Restek Corporation), H_2 carrier gas, average linear velocity 44 cm/s, flame ionization detection, autoinjection. Arachidonic acid, EPA, docosahexaenoic acid (DHA) and total n-3 fatty acid content (EPA + DHA + docosapentaenoic acid) are reported as the mean percentage of total plasma phospholipid fatty acyl methyl esters after correction, using response factors of authentic standards.

Calculated daily n-3 fatty acid intake was compared with plasma n-3 fatty acid levels using Spearman's rank correlation coefficient. A rectangular hyperbola [$y = ax/(1 + bx)$, where y = plasma phospholipid fatty acid level and x = dietary n-3 fatty acid intake] was fitted to the data for EPA and total n-3 fatty acids, and the coefficient of determination (R^2) was calculated. Patients were also divided into quartiles of daily dietary fish intake and the relation between plasma levels of n-3 fatty acids in each quartile of dietary fish intake was tested using a multiple sample comparison.

Daily dietary n-3 fatty acid intake was linearly related to plasma phospholipid levels of both total n-3 fatty acids ($r = 0.50$, $p < 0.01$) and EPA ($r = 0.45$, $p < 0.01$). Because the observed correlation is disproportionately enhanced by the small number of subjects with higher fish intake and higher concomitant plasma n-3 fatty acid levels, a series of hyperbolic curves were generated to

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TABLE I Dietary Fish Intake and Plasma Phospholipid N-3 Fatty Acid Levels by Quartiles

Quartile	No. of Pts.	Dietary N-3 Fatty Acid Intake (g/d)	N-3FA (% pph)	EPA (% pph)	DHA (% pph)	AA (% pph)
1st	9	0.05 ± 0.02	3.75 ± 0.97	0.64 ± 0.18	2.54 ± 0.7	10.07 ± 1.33
2nd	9	0.12 ± 0.03	4.02 ± 1.23	0.61 ± 0.18	2.77 ± 0.83	10.16 ± 2.17
3rd	9	0.18 ± 0.00	4.30 ± 1.35	0.77 ± 0.19	2.37 ± 0.83	9.90 ± 2.05
4th	9	0.47 ± 0.32	5.68 ± 1.67	0.99 ± 0.47	3.82 ± 1.06	10.08 ± 1.0
Newman-Keuls multiple sample comparison: 1st or 2nd vs 4th quartile			p <0.0005	p = 0.06	p <0.05	NS

AA = arachidonic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; N-3FA = n-3 fatty acids; NS = not significant; pph = plasma phospholipid fraction.

establish whether the relation between dietary n-3 fatty acid intake and plasma n-3 fatty acid levels might not be linear. The curve relating total n-3 fatty acids (Figure 1) was highly significant ($R^2 = 0.91, p < 0.0001$)*. An equally significant relation was observed between EPA and dietary n-3 fatty acid intake* ($R^2 = 0.84$, $p < 0.0001$)*. There was no significant relation between n-3 fatty acid intake and arachidonic acid levels* ($r = -0.003, p > 0.1$)*.*

Finally, plasma phospholipid n-3 fatty acid levels in each quartile of daily dietary fish intake were compared (Table I). Mean plasma phospholipid EPA and total n-3 fatty acid levels were significantly higher in the highest quartile of dietary n-3 fatty acid intake compared with the lowest quartile. No difference was found for arachidonic acid among quartiles of dietary n-3 fatty acid levels. No correlation was found between daily dietary n-3 fatty acids intake and other long-chain unsaturated fatty acids, including oleic and linoleic acid. Furthermore, daily saturated or polyunsaturated fatty acid intake did not appear to influence plasma n-3 fatty acid phospholipid levels.

The data presented in this study suggest that plasma phospholipid n-3 fatty acid levels accurately reflect chronic fish consumption. Traditionally, adipose tissue levels of fatty acids have been used as the best measure of long-term intake because they are the least influenced by short-term variation in fat intake compared with other tissues.[18,19] Fatty acid levels within plasma phospholipids, while not as stable as levels in adipose tissue, are relatively unaffected by daily changes in fatty acid intake.[20,21] The method described accurately detects very low levels of fatty acids in plasma phospholipids without requiring prior isolation of phospholipid-containing lipoproteins. Plasma phospholipid levels offer several practical advantages over more traditional methods of fatty acid quantification in terms of the amount of sample needed, the ease of sample collection (phlebotomy as compared to fat biopsy) and the preparation required for quantification by chromatography.

The selected population studied (CAD patients), and the fact that only one measurement of plasma levels was obtained, raises concerns about the accuracy and precision of the relation reported. Nevertheless, dietary n-3 fatty acid intake and plasma n-3 fatty acid levels were found to be significantly related by all 3 methods used to test their relation: linear regression, curve fitting analysis, and comparison by quartiles. A larger sample of individuals, including those without CAD, would presumably include a proportionately greater number of individuals with higher fish intake and would likely strengthen the observed relation. In terms of reproducibility, measurements of plasma fatty acids at several time points would only increase the correlation coefficient with dietary n-3 fatty acids as random error decreased.[22]

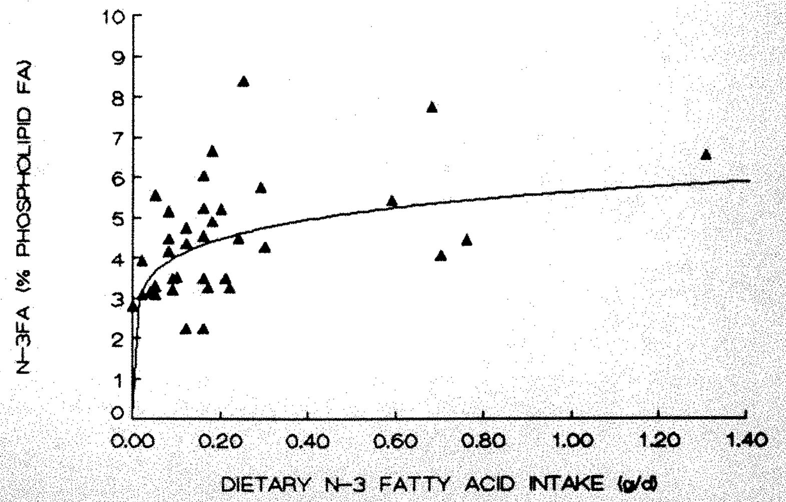

FIGURE 1. Comparison of dietary n-3 fatty acid (FA) intake with plasma phospholipid total n-3 fatty acid levels. Data were fitted to a best possible hyperbolic curve and coefficient of determination (R^2) calculated.

The data presented suggest that plasma phospholipid levels may prove to be a useful tool in ongoing or future epidemiologic studies as well as in clinical trials of dietary fish intake or fish oil supplementation.

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Creatine Kinase-MB Activity After Implantation of a Cardiac Pacemaker

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Identification of creatine kinase (CK) isoenzyme CK-MB has made an excellent improvement of the diagnosis of myocardial infarction.[1] Cardiac muscle contains relatively large amounts of CK-MB. CK-MB is also present in skeletal muscle. Injury to skeletal muscle may therefore result in elevation of "non-cardiac" CK-MB and cause difficulties in the diagnosis of myocardial infarction.[2,3] Elevation of CK-MB may also be expected in direct cardiac muscle injury, but previous studies reflecting this relation have shown only a slight increase in CK-MB isoenzyme activity.[4] This study evaluates total CK and isoenzyme CK-MB activity in patients undergoing cardiac pacemaker implantation. In this procedure there is injury to cardiac and skeletal muscle.

Seventeen consecutive patients gave informed consent for the study. There were 11 men and 6 women. Median age was 78 years (range 66 to 86). One patient was excluded because of development of acute myocardial infarction during the first day after pacemaker implantation. Three patients were excluded because of accidental intramuscular injection. After incision through the upper left pectoral muscle an Elema electrode was inserted through the left subclavian vein and directed to the right ventricle, where the electrode was implanted in a stable position. The procedure was finished with implantation of a battery in the pectoral muscle. Samples for enzyme analysis were taken from an antecubital vein before and 8, 16 and 24 hours after the procedure.

Total CK and CK-MB were assayed spectrophotometrically after the recommendation of Gerhardt and Waldenstrøm.[5] Upper reference limit for total CK and CK-MB is 270 and 6 U/liter, respectively. CK-MB values lower than 6 U/liter were not analyzed further and were accepted as 6 U/liter. CK-MB values at the lower end of activity measurements were not the aim of this study, since difficulties in the diagnosis of myocardial infarction appear at CK-MB values above 12 U/liter, which in Denmark is the discriminative limit for myocardial infarction. Statistical analysis consisted of a nonparametric procedure using Wilcoxon's test. A level of significance of $p < 0.05$ *was chosen.*

Before pacemaker implantation all 13 patients had total CK and CK-MB values lower than the upper reference limit. Total CK and CK-MB activity were signifi-

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cantly elevated ($p < 0.01$) at time 8, 16 and 24 hours compared to the values before the procedure. The changes were only slight. Median values for total CK were 70 U/liter (range 22 to 109), 107 U/liter (range 46 to 227), 100 U/liter (range 48 to 309) and 158 U/liter (range 48 to 251) at time 0, 8, 16 and 24 hours, respectively. Only 1 patient had a peak total CK value above the upper reference limit (>270 U/liter). Six patients had CK-MB values above the upper reference limit (>6 U/liter) but the elevations were slight and only 1 patient had a CK-MB activity above 12 U/liter. This patient had no signs of myocardial or cerebral infarction and had a total CK activity lower than the upper reference limit.

On the basis of the present report, cardiac pacemaker implantation results in only a minimal elevation of isoenzyme CK-MB activity. Thus, the procedure causes no difficulties in the diagnosis of myocardial infarction.

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From Various Kinds of Heart Rate Variability to Chronocardiology

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We wish to show that cardiologic variability can be examined with benefit by the concepts and computer methods of chronobiology, the science (logos) of life's (bios) time (chronos) structure. From heart rate data in a recent article,[1] dynamic end points are obtained to quantify health.[2] On a group basis, when conventional end points applied to 2 sets of electrocardiographic records fail to separate for sudden adult death, chronobiologic end points already do so.[2] Novel information not obtained by conventional location or dispersion indexes[3] can be provided by the computation of the circadian and other amplitudes.[4] Beyond sudden death after myocardial infarction, the importance of these amplitudes has been demonstrated in several additional cases of cardiologic interest[2]: (1) the amplitudes of several rhythmic components of systolic or diastolic blood pressure separate groups of human newborns with a positive versus negative family history of high blood pressure or cardiovascular diseases, or both, when the mean based on the same data does not do so; (2) in children ≥ 9 years old, the circadian amplitude and acrophase of blood pressure, but not the mean, separate groups at low or high risk of developing high blood pressure later in life; (3) at 15 years of age, the circadian amplitude of diastolic blood pressure, but not the mean, correlates with the thickness of the interventricular septum of the heart.

Rhythm indexes that serve on a group basis as classifiers and potential harbingers of a heightened cardiovascular risk will have to be individualized for use in the clinic as well as in research. The task on hand is to assess the relative merits of the various uses of time-unqualified model-free end points[5,6] when they work versus the use of chronobiologic indexes, such as the rhythm characteristics of the acceptable (in this sense "normal") heart rate. In this context, a single 24-hour cycle from a circadian viewpoint corresponds to the radial pulse based on a single heartbeat. Chronobiologic recorders and analyzers that store and analyze the data as one goes, already available in chronobiologic pacemaker prototypes, may constitute a step in the direction of obtaining sufficient data for preventive rather than "after-the-fact" therapy.

When viewed on original records, circadian changes can be very irregular. This irregularity can be smoothed by averaging. Circadian changes in heart rate and blood pressure can then be displayed in time plots, time-macroscopically.[1-3] Statistical location indexes, such as hourly means over 24 hours, can be used to illustrate the changes in the variables themselves and also in the variability of a given body function, estimated as a dispersion index, such as the standard deviation or the standard error of measurements collected over consecutive hourly spans. Graphs of both hourly means and standard errors along the scale of 24 hours have been published for subjects with a seemingly acceptable or elevated blood pressure[3] and analyzed[4] by the fit of a 24-hour cosine curve and harmonics performed with the precautions of the time-microscopic technique of the cosinor.[2] Rhythms, in a strict sense, can be defined as algorithmically formulated recurrent changes validated by inferential statistical means. Recently, differences in the circadian timing of changes in heart rate and its variability were reported in the light of paired t tests and coefficients of variation applied to electrocardiographic records of 22 healthy vol-

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From the Chronobiology Laboratories, University of Minnesota, 420 Washington Avenue, SE, Minneapolis, Minnesota 55455, Medtronic Inc., 7000 Central Avenue, NE, Minneapolis, Minnesota 55432, Karolinska Institute, Stockholm, Sweden, and the University of Milan, Milan, Italy. This study was supported in part by Grant GM-13981 from the U.S. Public Health Service and Grant HL-40650 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and by the Dr.h.c. Dr.h.c. Earl Bakken Fund and the Dr. Betty Sullivan Fund, Minneapolis, Minnesota. Manuscript received March 8, 1990; revised manuscript received May 25, 1990, and accepted May 28.

TABLE I Improvement over 1-Component Model from 2- and 3-Component Models Fitted to Healthy Human Subjects, Heart Rate Mean (HR) and Standard Deviation (SD)

Trial Period (hrs)	PR	Amplitude ± SE	Acrophase, φ ± SE	[Bathyphase]	p Value* Var Hom
HR (beats/min)					
1-component model					
24	83	11.4 ± 1.1	−249° ± 6	[−69°]	<0.001
2-component model					
24	83	11.4 ± 0.7	−249° ± 4		
12	11	4.1 ± 0.7	−331° ± 10		
Overall	94	12.3	−204°	[−24°]	<0.001
3-component model					
24	83	11.4 ± 0.4	−249° ± 2		
12	11	4.1 ± 0.4	−331° ± 6		
8	4	2.7 ± 0.4	−68° ± 9		
Overall	98	13.8	−260°	[−80°]	0.819
SD (RR; ms)					
1-component model					
24	69	11.0 ± 1.6	−72° ± 8	[−252°]	<0.001
2-component model					
24	69	11.0 ± 1.0	−72° ± 5		
12	20	5.9 ± 1.0	−168° ± 10		
Overall	88	13.6	−80°	[−260°]	<0.001
3-component model					
24	69	11.0 ± 0.6	−72° ± 3		
12	20	5.9 ± 0.6	−168° ± 5		
8	9	3.9 ± 0.6	−238° ± 8		
Overall	97	15.0	−80°	[−260°]	0.321

* p values for rejection of zero amplitude assumption are invariably <0.001 for each component in the 3 models fitted (not shown). As to p values from test of assumptions underlying the multiple component model, a $p > 0.05$ validates the fitted model, whereas a $p < 0.05$ provides information concerning data departure from underlying assumptions. The normality of residuals was tested by a Shapiro-Wilk test ($p > 0.05$ in each case, not shown). When a regression diagnostic test yields p values <0.05, transformations or alternate models are to be considered. The addition of a third component, in the case of the data analyzed herein satisfies the test of homogeneity of variance. Goodness of fit tests of the model could not be performed because replicates were not available (a limitation to analyses based only on published data taken off the chart).

Mean and standard deviation of cardiac cycle lengths calculated for 5-minute intervals and averaged hourly over 24 hours. Adapted with permission from Huikuri et al.[1]

Acrophase and bathyphase are the lag from midnight of the crest and trough time of the model fitted to the data, respectively, expressed in degrees, with 360° equated to 24 hours.

SE = standard error; var hom = homogeneity of variance.

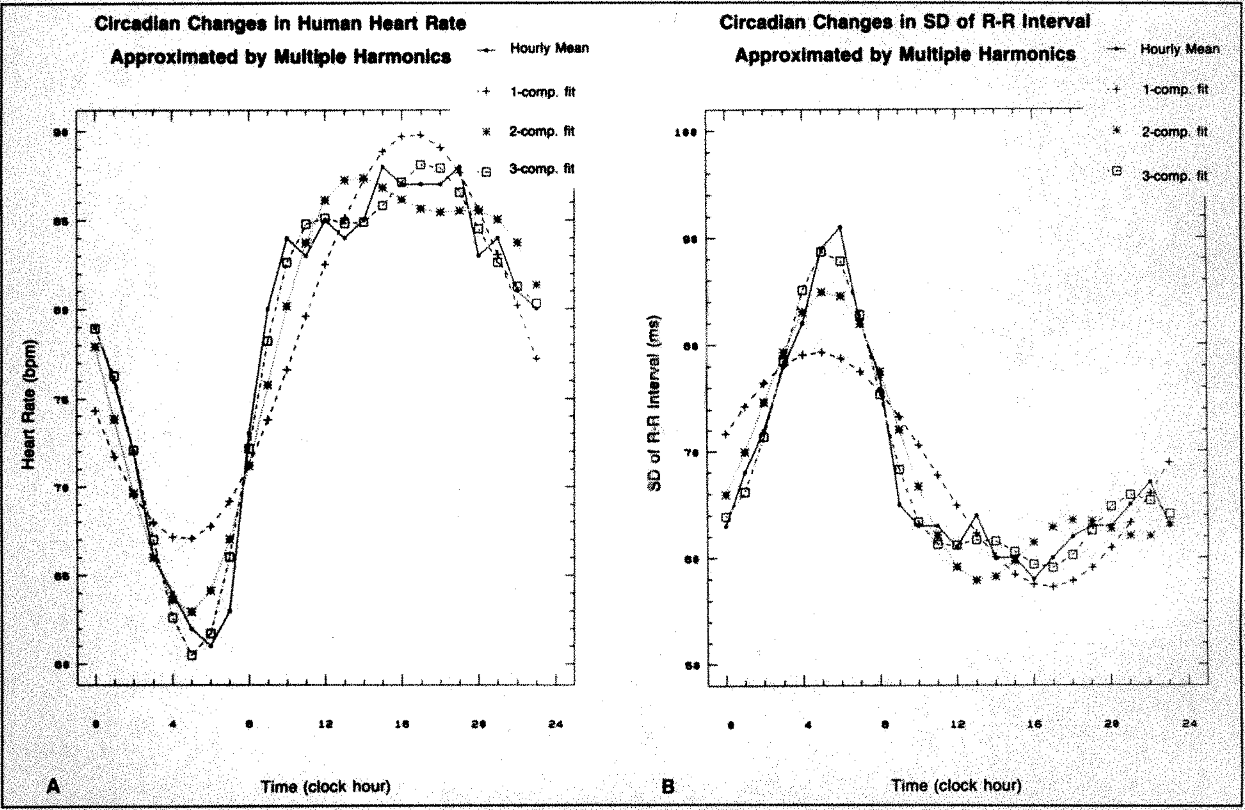

FIGURE 1. Circadian rhythm in *(A)* heart rate (in beats/min) and in *(B)* standard deviation of RR intervals (in milliseconds) approximated by a 24-hour cosine curve alone or with 1 (12-hour) or 2 (12- and 8-hour) harmonic components; original data of Huikuri et al.[1] taken off published graph; mean ± standard deviation of cardiac cycle lengths calculated for 5-minute intervals and averaged hourly over 24 hours.

unteers, each contributing data for 2 or 3 twenty-four-hour spans.[1] Heart rate variability was expressed as the standard deviation of normal cardiac cycle lengths during successive 5-minute intervals, averaged hourly and displayed over the course of 24 hours in parallel with hourly heart rate means.

Cosinor analyses of averages taken off the published graph[1] (Figure 1) validate a circadian rhythm for heart rate and its variability ($p < 0.001$), accounting for 83 or 69% of the total variance, respectively (Table I). These analyses derive rhythm characteristics revealing, when the data are expressed as a percentage of the mean, a difference in timing ($p < 0.001$) in the absence of a difference in amplitude ($p = 0.571$) between the 2 variables. As a measure of timing, the acrophase is expressed in degrees as the lag from midnight (0°) of the crest time in the cosine function fitted to the data (360° = 24 hours, 15° = 1 hour and 1° = 4 minutes). Whereas the heart rate "peaks" at −249° ± 6° from midnight (16:36 ± 0:24), the standard deviation of the RR intervals peaks almost in antiphase, at −72° ± 8° (04:48 ± 0:32) from midnight (Figure 1). The consideration of the second (12-hour) and third (8-hour) harmonics further improves the fit, accounting for 98 and 97% of the total variance without unduly altering the acrophase estimates (Table I). Such end points complement other approaches to heart rate variability.

Kleiger et al[5] define variability as "... the standard deviation of all normal RR intervals in a 24-hour continuous electrocardiogram recording ...," whereas Rich et al[6] calculate it as "... 5-minute means of sinus cycle lengths," assessed in 24-hour ambulatory electrocardiograms. The association of an increased mortality after a myocardial infarction with a reduced heart rate variability (standard deviation of RR intervals <50 ms) reported by Kleiger et al[5] suggests an association with the circadian amplitude of heart rate. The standard deviation derived from 24-hour recordings may indeed be considered as a rough approximation of the circadian amplitude. This impression is supported by a statistically significant correlation between these 2 indexes for a population of 40 clinically healthy men, 20 to 60 years of age, monitored at 7.5-minute intervals for 24 hours on 2 occasions[7,8] (data averaged hourly, $r = 0.946$, $p < 0.001$; Figure 2).

It is important to specify how heart rate variability is assessed. A reduced heart rate variability (computed on 5-minute spans) was also found by Rich et al[6] to correlate with mortality in patients undergoing elective coronary angiography, but not with other clinical, angiographic or Holter variables. When computed over the whole 24-hour span by Kleiger et al,[5] it did so, although on a different sample. A difference between the 2 approaches to compute heart rate variability may contribute to these results, relating to different (circadian versus ultradian) regions of the spectrum. When computed over hourly intervals, the standard deviation is likely to undergo circadian changes related to the wave form of the circadian rhythm in heart rate itself: a larger variability is anticipated and found around awakening, when heart rate changes rather abruptly from low nightly to much higher daily values (the actual transition usually starts earlier, but any anticipatory rise preceding awakening and the transition in the evening are usually smoother and slower). These considerations further credit the results of Huikuri et al[1]: By computing the standard deviation of RR intervals over 5-minute spans and averaging hourly, the interference by the circadian wave form of heart rate with the variability of RR intervals as such is reduced. The antiphase between the rhythms in heart rate and its variability is thus unlikely to be a consequence of the wave form of the circadian heart rate rhythm.

To check on the properties of the standard deviation as a function of the interval over which it is calculated and to rule out any artifact in the rhythmicity of heart rate variability reported by Huikuri et al,[1] computer simulations were performed. Beat-to-beat heart rates over 24 hours were simulated using the 3-component model of Table I, contaminated with a normally distributed error term of zero mean and constant variance. As expected, the standard deviation calculated over the whole 24-hour span approximates the circadian amplitude: that which is calculated over consecutive hourly spans undergoes a circadian rhythm with an acrophase around awakening, whereas that calculated over consecutive 5-minute spans and averaged hourly does not exhibit similar changes. The fact that the 2 rhythms have an almost opposite timing, as reported for heart rate[1] and earlier for blood pressure,[4] is also in keeping with the negative correlation between heart rate variability and heart rate itself, re-

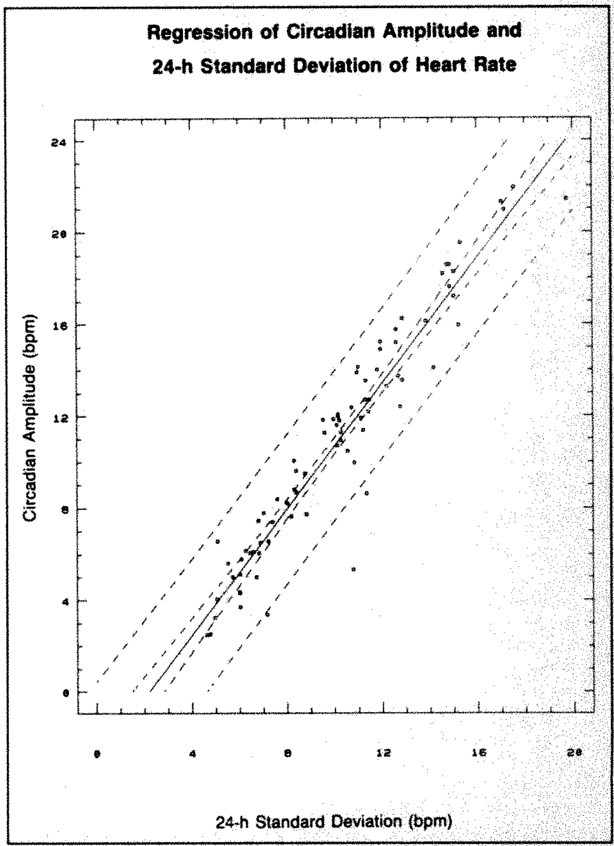

FIGURE 2. Circadian amplitude correlates positively ($r = 0.946$; $p < 0.001$) with the overall standard deviation. Computations from hourly averages of heart rates measured every 7.5 minutes over 24 hours on 40 men, 20 to 60 years of age, monitored on 2 occasions.[7,8]

ported by both Kleiger et al[5] and Rich et al,[6] who, without reference to timing, derive benefit from using data covering an entire circadian cycle.

Aberrant heart rate variability may reflect alterations in cardiac autonomic tone, which could predispose to the development of lethal arrhythmias.[6] In this context, the quantification of a time structure in heart rate variability serves for facilitating the recognition of any early deviation that may point to an increased cardiovascular disease risk. Beyond the context of a mechanism for the inverse relation between heart rate and its variability and its bearing on sudden cardiac death, an earlier finding made with chronobiologic methods gains in interest: An increased incidence combined with an amplified, phase-shifted circadian rhythm of premature ventricular beats in a 24-hour electrocardiogram performed after a myocardial infarction characterizes patients who die suddenly within 5 years compared with those who survive (Figure 3). The groups were separated by considering the features of the circadian rhythm, but not when only the average 24-hour incidence of ventricular premature beats was used. Variability without or preferably with chronobiometry[2] may add another dimension, unavailable for the retrospective Figure 3 analyses. The time structure of variability within the physiologic range remains the challenge of an already rewarding chronocardiology (Figure 3). The incidence of infant as well as adult sudden death reveals a spectrum of population rhythms that should prompt research into the factors underlying the difference in pattern illustrated in Figure 3.

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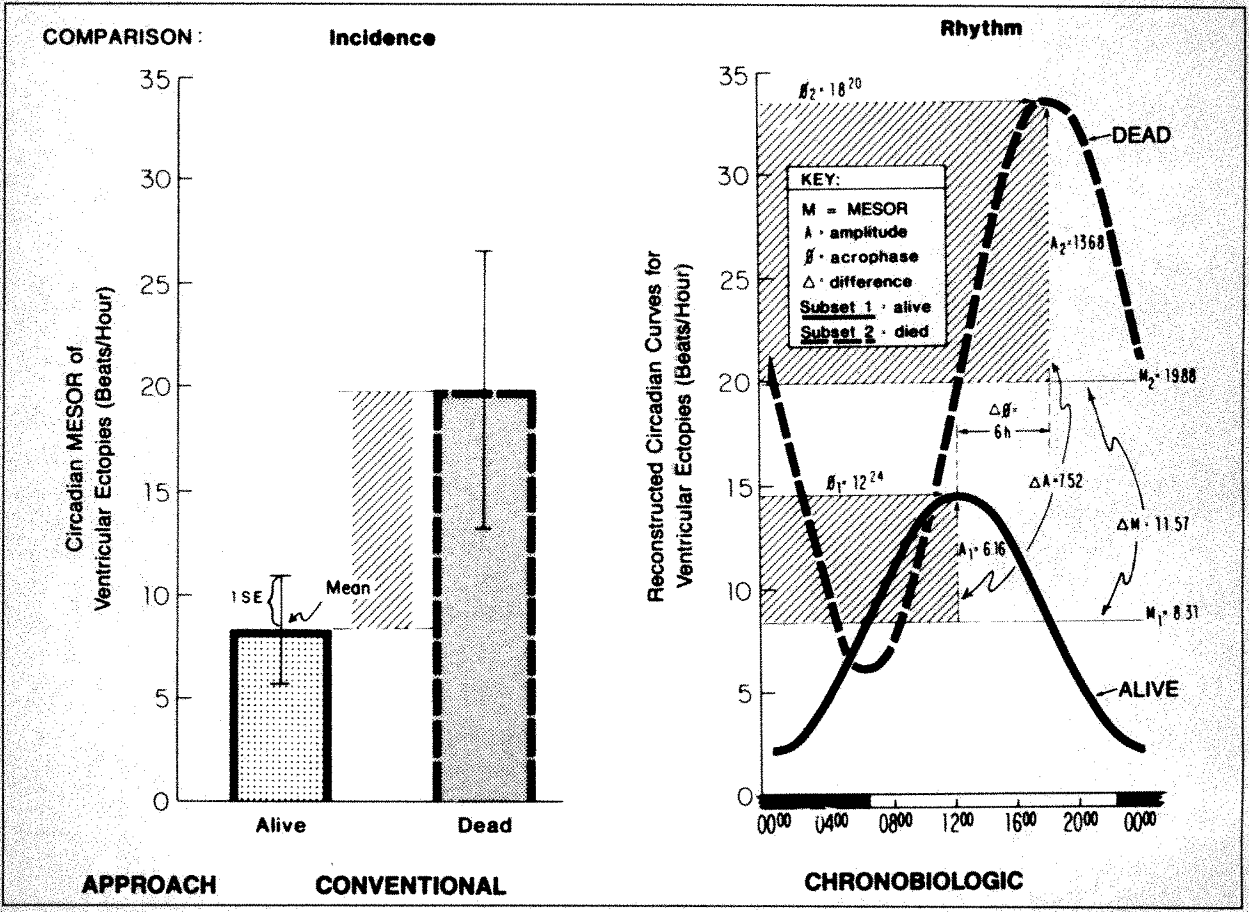

FIGURE 3. Chronobiologic analyses based on the circadian amplitude and acrophase in addition to the 24-hour mean value of hourly incidence of ventricular ectopies in 24-hour ECG succeed ($p = 0.002$) in separating groups of patients who are dead or alive 5 years after a myocardial infarction when the conventional approach *(left)* based only on the 24-hour mean does not ($p = 0.084$). Adapted with permission from Orth-Gomer K, Cornélissen G, Halberg F, Sothern R, Åkerstedt T. Relative merits of chronobiologic vs. conventional monitoring of ventricular ectopic beats. In: Halberg F, Reale L, Tarquini B, eds. Second International Conference, Medico-Social Aspects of Chronobiology, Florence, Oct. 2, 1984. Rome: Istituto Italiano di Medicina Sociale, 1986;767–770.

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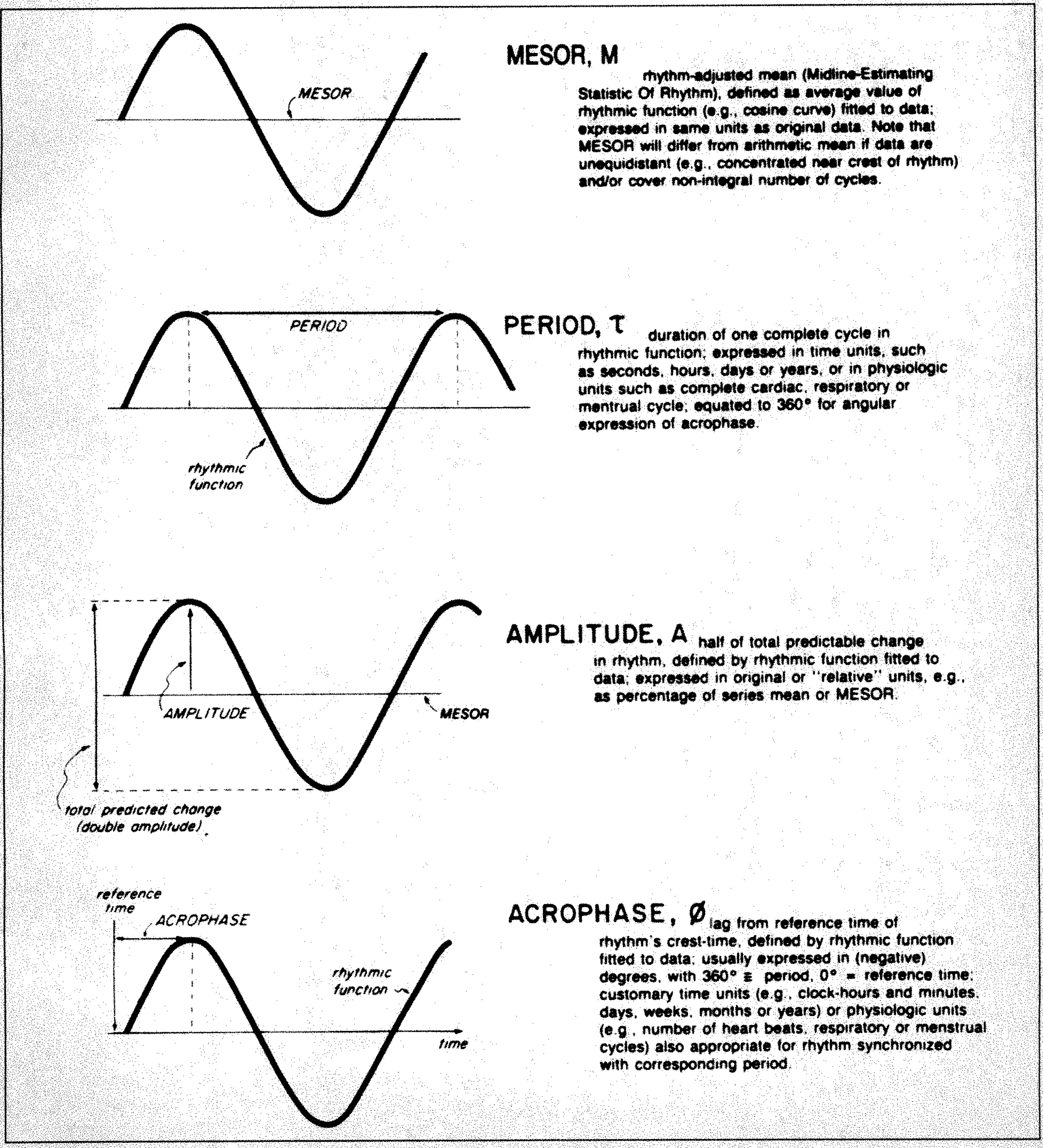
APPENDIX

Definition of Terms (Figure 4)

Cosinor: statistical summary with display on polar coordinates of rhythm characteristics. The single cosinor adjusts, by least squares, a rhythmic function with a presumed period (anticipated on the basis of prior experience) to a data series, thus providing point-and-interval estimates of MESOR, amplitude and acrophase; statistical significance of the fitted function is checked by means of a zero-amplitude test. The population mean cosinor derives inferences for the population from parameter estimates obtained from 3 or more individuals or from 3 or more time series obtained from the same individual.

MESOR: an acronym for the midline-estimating statistic of rhythm; rhythm-adjusted mean, defined as the average value of a rhythmic function fitted to the data. The MESOR differs from the arithmetic mean whenever the data are nonequidistant and/or cover a non-integral number of cycles, in which case the



MESOR, M rhythm-adjusted mean (Midline-Estimating Statistic Of Rhythm), defined as average value of rhythmic function (e.g., cosine curve) fitted to data; expressed in same units as original data. Note that MESOR will differ from arithmetic mean if data are unequidistant (e.g., concentrated near crest of rhythm) and/or cover non-integral number of cycles.

PERIOD, τ duration of one complete cycle in rhythmic function; expressed in time units, such as seconds, hours, days or years, or in physiologic units such as complete cardiac, respiratory or mentrual cycle; equated to 360° for angular expression of acrophase.

AMPLITUDE, A half of total predictable change in rhythm, defined by rhythmic function fitted to data; expressed in original or "relative" units, e.g., as percentage of series mean or MESOR.

ACROPHASE, ϕ lag from reference time of rhythm's crest-time, defined by rhythmic function fitted to data; usually expressed in (negative) degrees, with 360° ≡ period, 0° = reference time; customary time units (e.g., clock-hours and minutes, days, weeks, months or years) or physiologic units (e.g., number of heart beats, respiratory or menstrual cycles) also appropriate for rhythm synchronized with corresponding period.

MESOR is usually more accurate (i.e., associated with less bias from sampling). When data are equidistant, the MESOR is also usually more precise (i.e., associated with a smaller standard error) if the time series undergoes a rhythmic change.

Period: duration of 1 complete cycle of the rhythmic function.

Amplitude: half the total predictable change defined by the rhythmic function fitted to the data.

Acrophase: lag from a given reference time (such as midnight) of the rhythm's crest time, defined by the rhythmic function fitted to the data. The acrophase is expressed in (negative) degrees, with 360° equated to the period length and 0° taken as the reference time. In the case of circadian (24-hour) rhythms, when 0° is chosen at midnight, the acrophase can also be expressed in hours and minutes.

Circadian: relating to biologic variations or rhythms with a frequency of 1 cycle in 24 ± 4 hours.

Ultradian: relating to biologic variations or rhythms with a frequency higher than circadian (i.e., with a period shorter than 20 hours).

Harmonic: any periodic function with a given period, τ, can be considered as the sum of a constant term (MESOR) and cosinusoidal functions with periods τ, $\tau/2$, $\tau/3$, . . ., with given amplitudes and acrophases. The component with a period τ is the fundamental or first-order harmonic. The component with a period τ/n is the nth harmonic, where $n = 2, 3, \ldots$

Prognosis and Predisposing Factors for Essential Malignant Hypertension in Predominantly Black Patients

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Fifty years ago, the average survival of patients with malignant hypertension was only 10.5 months. When antihypertensive treatment became available in the 1950s, incidence and prognosis improved dramatically. Recently, a 5-year patient survival of >70% among white patients was reported.[1] Malignant hypertension is now relatively rare and is more prevalent among black[2] than among white patients.[1] We studied the outcome of malignant hypertension in predominantly black patients seen at an urban inner city hospital between 1985 to 1988, because little recent information exists about the prognosis of this disease in black patients. We also investigated factors that might have contributed to the development of malignant hypertension in our patients.

We used computerized diagnosis files to review the medical records of patients who were admitted to the hospital with severe hypertension (diastolic blood pressure >130 mm Hg) for the years 1985 through 1988. Twenty patients who met the World Health Organization criteria (grades III and IV hypertensive retinopathy) for malignant hypertension[3] qualified for inclusion in the study. All had essential malignant hypertension on the basis of history, examination and routine investigations. The medical records were used to determine race, history of hypertension, antihypertensive drug treatment, cigarette smoking, and alcohol and illicit drug use.

Clinical characteristics of our patients are listed in Table I. Eleven men and 9 women (mean age 42.5 years) were studied. Eighteen patients were black. Mean systolic and diastolic blood pressures were 233 and 156 mm Hg, respectively. Serum creatinine level was elevated (>1.5 mg/dl) in 18 patients. Mean serum creatinine level was 5.4 mg/dl (range 1.1 to 30). Follow-up serum creatinine level, determined in 15 patients, had increased (>1 mg/dl) in 6, decreased in 4 and did not change in 5. Left ventricular hypertrophy by electrocardiogram or echocardiogram was present in 15 of the 19 patients studied. All except 2 patients were symptomatic at the time of diagnosis. The most common complaints were headache, visual symptoms, nausea or vomiting, and dizziness.

Seventeen patients gave a history of having hypertension (mean duration 5.8 years, range 1 to 25). All had received antihypertensive drug treatment previously but 16 had discontinued it for periods of 3 days to 5 years. Seventeen of 19 patients had habitually smoked cigarettes within the 2 months before hospitalization. Fifteen patients gave a history of illicit drug use or ingestion of

TABLE I Clinical Features in 20 Patients with Malignant Hypertension

Case	Age (yr) & Sex	BP (mm Hg) (s/d)	Duration of SH (yr)	Last Dose of Antihypertensive Medication	Outcome
1	26M	220/160	U	Never	Hemodialysis
2	27F	200/140	2	2 weeks	Transplant
3	31F	240/160	1	2 months	Alive
4	31F	200/140	1	1 week	Hemodialysis
5	34M	260/184	1	5 days	Dead
6	35M	230/160	7	2 years	Alive
7	35F	220/180	1	2 weeks	Dead
8	35F	230/140	5	3 weeks	Alive
9	37M	240/160	1	"weeks"	Hemodialysis
10	38M	210/160	7	4 years	Hemodialysis
11	39F	260/164	5	"weeks"	Dead
12	43M	210/140	3	"weeks"	Hemodialysis
13	46F	270/160	U	Never	Alive
14	46F	180/132	6	4 years	Alive
15	54M	260/160	3	3 days	Dead
16	56M	240/160	15	1 week	Alive
17	56F	250/170	15	5 years	Alive
18	59M	260/140	U	Never	Alive
19	61M	240/170	25	Current	Dead
20	61M	240/140	18	"years"	Dead

BP = blood pressure; s/d = peak systole/end diastole; SH = systemic hypertension; U = unaware.

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excessive amounts of alcohol, or both. Details of usage were as follows: cocaine (7 patients), alcohol (8 patients), heroin (4 patients) and phencyclidine (1 patient).

Follow-up period ranged from 1 to 54 months (mean 16). Six patients died within 3 to 24 months (mean 9). The causes of deaths were: sudden cardiac death (2 patients), ruptured aorta (1 patient), uremia and sepsis (1 patient), and hypertensive encephalopathy (2 patients). Two patients required hemodialysis acutely. In 1, dialysis could be discontinued and his serum creatinine at 30 months was 3.5 mg/dl. The second patient remains on hemodialysis 52 months later. Five other patients developed progressive renal failure and entered a long-term hemodialysis program 17 to 54 months (mean 34) after malignant hypertension was diagnosed. One of these subsequently received a renal allograft, which continues to function 24 months later. Twelve- and 54-month patient survival were 76 and 71%, respectively. The corresponding figures for renal survival (i.e., patients surviving with their native kidneys) were 71 and 43%, respectively.

Sparse information exists regarding factors that might predispose to the development of malignant hypertension. Suboptimal therapeutic compliance is a major problem in hypertensive patients. In our study, 16 of 17 (94%) patients had discontinued their antihypertensive treatment before the development of malignant hypertension. This could have resulted in progression to the malignant phase because of rebound phenomenon, or more likely due to the high pressure that had probably continued after cessation of treatment.

Interestingly, cigarette smoking was 2.5 times the incidence rate expected for this population[4] ($p < 0.005$). Epidemiologic studies failed to show any relation between cigarette smoking and the level of blood pressure. It has been suggested that cigarette smoking may predispose to the development of the malignant phase in a patient who is already hypertensive.[5]

A large increase in systemic blood pressure may occur during cocaine use in conjunction with preexisting systemic hypertension.[6] One of our patients (case 5) required repeated hospitalizations for episodes of severe hypertension that culminated in a malignant phase and was temporally related to cocaine use. Moreover, persons who consume more than 2 to 3 alcoholic drinks per day tend to have higher blood pressures. However, we are unaware of any studies linking cocaine or heavy alcohol use to malignant hypertension.

The major cause of mortality in malignant hypertension was uremia. Aggressive treatment with antihypertensive drugs in conjunction with dialysis treatment have lead to stabilization and even reversal of uremia in some cases. As a result, the number of patients dying from irreversible renal failure has been reduced and overall patient survival has improved.[1]

Strategies aimed at the prevention and treatment of hypertension may be a key step toward a reduction in the risk of developing malignant hypertension. Despite the difficulties of achieving this goal, the benefits are multifaceted, including a reduction in cost as a result of fewer hospitalizations and less complications. Provision of better access to adequate health care facilities is essential if these expectations are to be realized. Finally, we are in an era in which available funds are limited. Since the enactment of legislation in 1972, physicians are required to provide treatment for end-stage renal disease to all patients with Medicare coverage unless therapy is medically contraindicated. Even a small decrease in the end-stage renal disease program pool could effect significant reduction in the 2 billion dollar program costs. The issue of cost-effectiveness and the problems arising out of the escalating costs of health care delivery to the inner city poor will require careful evaluation.

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RV$_6$:RV$_5$ Voltage Ratio in Systemic Hypertension

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A ratio between the R-wave voltage of leads V$_6$ and V$_5$ >1.0 has been reported to be useful in the diagnosis of left ventricular (LV) hypertrophy in different clinical situations.[1] Recently, Spodick and Koito[2] studied the sensitivity and specificity of additional cutpoints <1.0 in cardiomyopathy and valvular heart disease, and showed that the sensitivity of this index is lesion-related. Nevertheless, to our knowledge, there has been no study about the usefulness of this ratio in systemic hypertension. Given the frequent use of the electrocardiogram in the study of the hypertensive patient to discover LV hypertrophy, we think that it may be interesting to study the sensitivity and specificity of different cutoff points of this ratio in systemic hypertension. Further, a comparison of this in-

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TABLE I Results of RV6:RV5 Voltage Ratio and Other Criteria

ECG Criteria	Patients with LV Mass >215 g (n = 46)	Patients with LV Mass ≤215 g (n = 28)	Sensitivity	Specificity	Accuracy
RV_6:RV_5					
>0.1	4	5	0.08	0.82	0.32
>0.95	7	7	0.15	0.75	0.38
>0.90	7	7	0.15	0.75	0.38
>0.85	13	11	0.28	0.60	0.41
>0.80	22	13	0.47	0.53	0.50
>0.75	33	16	0.67	0.42	0.61
>0.70	39	20	0.84	0.28	0.64
>0.65	41	22	0.89	0.21	0.64
>0.60	46	28	1	0	0.62
RaVL >11 mm	5	2	0.11	0.93	0.42
RV_5-V_6 + SV1 >35 mm	8	2	0.17	0.93	0.46
Largest R + S >45 mm	3	0	0.06	1	0.42
R-E Score ≥5	5	0	0.11	1	0.45

ECG = electrocardiographic; LV = left ventricular; Largest R + S = Largest R wave plus largest S wave in precordial leads; RaVL = R wave amplitude in lead aVL (10 mm = 1 mV); R-E Score = Romhilt-Estes point score system; RV_5-RV_6 + SV_1 = R-wave amplitude in V_5 or V_6 (the largest) plus S-wave amplitude in lead V_1 (10 mm = 1 mV).

dex with other well-known and frequently used voltage criteria[3] will be worthwhile.

M-mode and 2-dimensional echocardiograms and 12-lead electrocardiograms (10 mm = 1 mV) were obtained in 74 consecutive patients (in order of when they were diagnosed) with essential hypertension (blood pressure ≥140/90 mm Hg) seen in a general hospital. Patients with heart diseases (valvular heart disease, cardiomyopathy, coronary artery disease, and so forth) and inconclusive echocardiograms were excluded, as well as subjects with left bundle branch block, other intraventricular conduction defects or preexcitation in the electrocardiogram. LV mass was calculated using the Penn conventions.[4] *LV mass (g), = 1.04 [(LVID + PWT + VST)*^{3} *− LVID]*^{3} *− 13.6, where LVID is end-diastolic left ventricular internal dimension, PWT is end-diastolic posterior wall thickness and VST is end-diastolic ventricular septal thickness. An LV mass ≤215 g was considered normal.*[3,4] *The* RV_6:RV_5 *voltage ratio, as well as R-wave amplitude in aVL (normal ≤11 mm), R wave in* V_5 *or* V_6 *+ S wave in* V_1 *(normal ≤35 mm), largest R wave + largest S wave in precordial leads (normal ≤45 mm) and the total points in the Romhilt-Estes score system (normal <5 points) were measured in the electrocardiograms.*[3]

The blood pressure was 157 ± 15 mm Hg (systolic) and 100 ± 5 mm Hg (diastolic). Among the 74 patients (27 men and 47 women), aged 49 ± 11 years, an LV mass >250 g was found in 46 (62%). The LV mass was 258 ± 95 g. The RV_6:RV_5 *ratio was 0.82 ± 0.22. The sensitiv-*

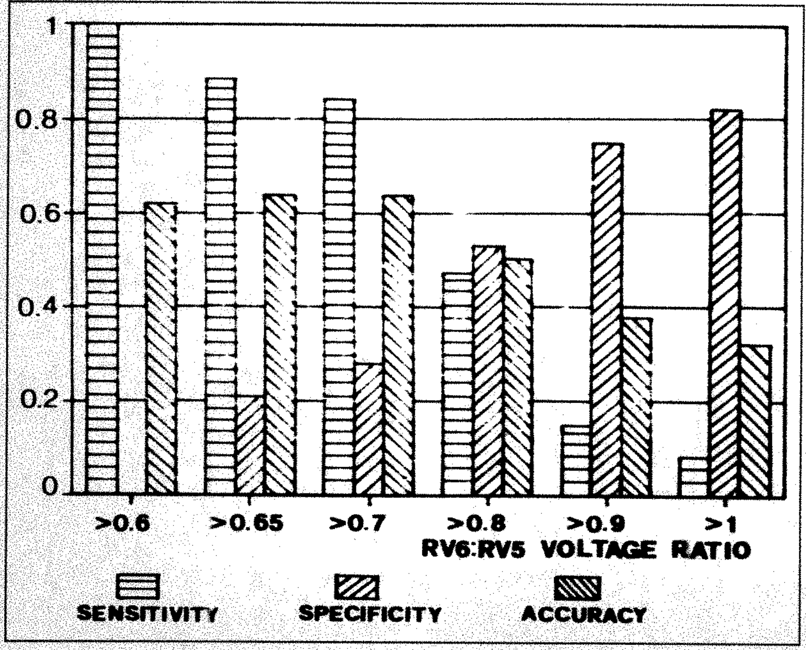

FIGURE 1. The sensitivity and specificity of each cutoff RV_6:RV_5 ratio is shown. As the ratio increases, the specificity increases but the sensitivity decreases. The cutoff point >0.65 gives the best accuracy and a good sensitivity for the diagnosis of left ventricular hypertrophy in hypertension.

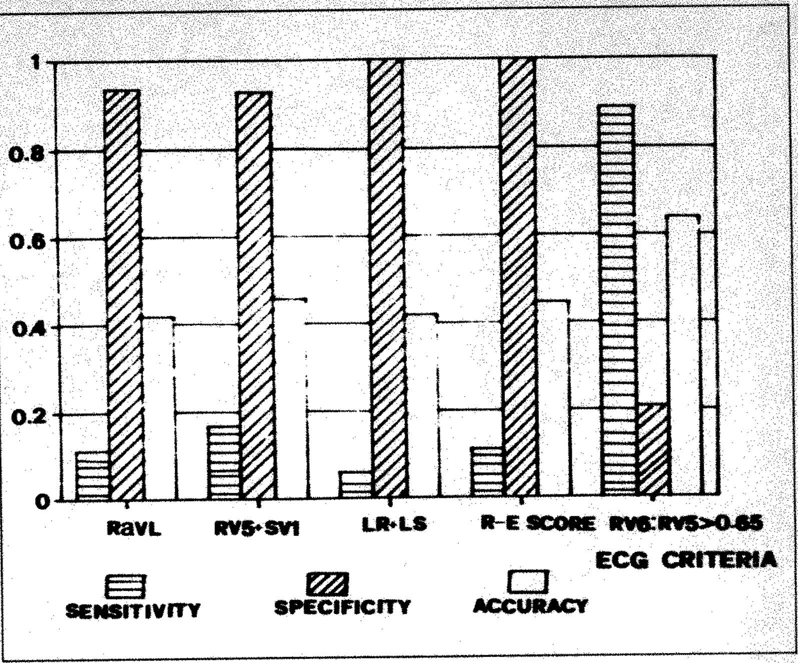

FIGURE 2. The sensitivity and specificity of different electrocardiographic (ECG) criteria of left ventricular hypertrophy are compared. Because the sensitivity and the accuracy of the RV_6:RV_5 ratio >0.65 are much higher, this index is the best for screening of left ventricular hypertrophy in the hypertensive patient. LR + LS = largest R wave plus largest S wave (amplitude) in precordial leads; R-E score = Romhilt-Estes point score system; RaVL = R-wave amplitude in aVL; RV_5 + SV_1 = R-wave amplitude in lead R_5 or R_6 (the largest) plus S-wave amplitude in lead V_1; RV_6:RV_5 >0.65 = RV_6:RV_5 voltage ratio >0.65.

ity, specificity and accuracy of each cutoff point studied in the RV_6:RV_5 voltage ratio, and other measurements, are listed in Table I and shown in Figure 1. A comparison among RV_6:RV_5 >0.65 and other criteria is shown in Figure 2. As the ratio RV_6:RV_5 increases, the specificity increases at the expense of sensitivity. A ratio RV_6:RV_5 >0.65 yields the best accuracy for these patients, for whom a technique with high sensitivity is needed. A ratio RV_6:RV_5 >0.60 has the best sensitivity but poorer specificity and a lesser accuracy. The other criteria have a very high specificity but a sensitivity far less than the RV_6:RV_5 voltage ratio.

According to our data, a ratio between the R-wave voltage of leads V_6 and V_5 >0.65 is a simple and useful index of LV hypertrophy in the hypertensive patient, with a sensitivity of 89%, a specificity of 21% and an accuracy of 64%. This index is much better than most frequently used ones for the study of cardiac hypertrophy in systemic hypertension, given that a highly sensitive technique is needed for screening. This is more important if we realize that electrocardiographic LV hypertrophy has independent prognostic significance in hypertension.[5]

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Transesophageal Color Flow Doppler and Echocardiographic Features Of Normal and Regurgitant St. Jude Medical Prostheses in the Mitral Valve Position

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Transthoracic echocardiography and color flow Doppler have been shown to be of value in evaluating regurgitant St. Jude Medical (SJM) prostheses in the aortic valve position.[1] These studies have emphasized the limitations of this technique in diagnosing SJM mitral regurgitation because of flow masking and signal attenuation produced by the echo-reflective metallic valves.[2] Transesophageal echocardiography and color flow Doppler overcome these problems and show promise in evaluating normal functioning and regurgitant SJM mitral valves.[3,4] This report describes our transesophageal ultra-

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sound experience with 28 normal functioning and 8 regurgitant SJM prostheses in the mitral valve position.

Transthoracic and transesophageal echocardiography and color flow Doppler studies were performed in 36 patients with SJM prostheses in the mitral position by previously reported techniques.[5] At transesophageal study, the valves had been in place from 1 day to 42 months (mean 12 months). Of the 36 transesophageal valve studies, 28 appeared normal and 8 had features of valve regurgitation. In the 8 patients, regurgitation was substantiated by cardiac catheterization and angiography in 4, and valve replacement surgery in 5. The prosthetic valve replacement surgery was performed within 8 days of transesophageal study. In 12 patients the transesophageal study was performed in the operating room, whereas in 24 others the tests were performed on awake patients.

All valves were evaluated by color flow Doppler for the presence or absence of valve regurgitation. The color flow gain and reject settings were adjusted to just below the level at which background noise was seen. The color flow Doppler regurgitant jet length, width, duration, location, shape and color characteristics were evaluated by playing back the video tape and frame-by-frame analysis. The extent of the prosthetic mitral valve regurgitation jet by transthoracic and transesophageal color flow Doppler was semiquantitated by relating it to the left atrial chamber.[6]

Transesophageal color flow Doppler demonstrated 3 regurgitant jets (Figure 1) in all 28 normal functioning SJM mitral valves. The jet length varied from 1 to 3.5 cm and the width from 0.5 to 1.5 cm in awake patients and from 0.6 to 2.5 cm and 0.4 to 1 cm, respectively, in anesthetized patients. In all the patients, the regurgitant jet was holosystolic, centrally located and occupied <50% of the left atrial chamber. Occasional color flow reversal and mosaic pattern limited to a small area of the jet was observed. In awake patients there was variation in the length, width and degree of color flow reversal and turbulence within the same jet and in the same persons at different times of the procedure.

Both transesophageal and transthoracic 2-dimensional echocardiography of normal functioning St. Jude mitral valves demonstrated multiple echoes emanating

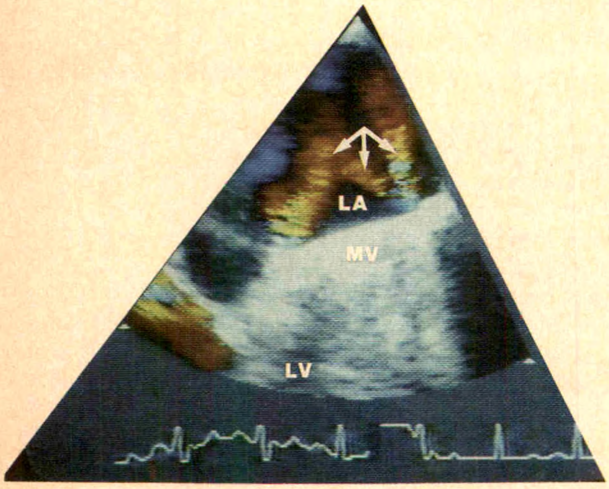

FIGURE 1. Transesophageal color flow Doppler of a patient with "physiologic" mitral regurgitation. Note the 3 regurgitant jets *(arrows)*, which are of narrow width, central, and have color flow reversal and mosaic features limited to only 1 of 3 jets. LA = left atrium; LV = left ventricle; MV = St. Jude mitral valve.

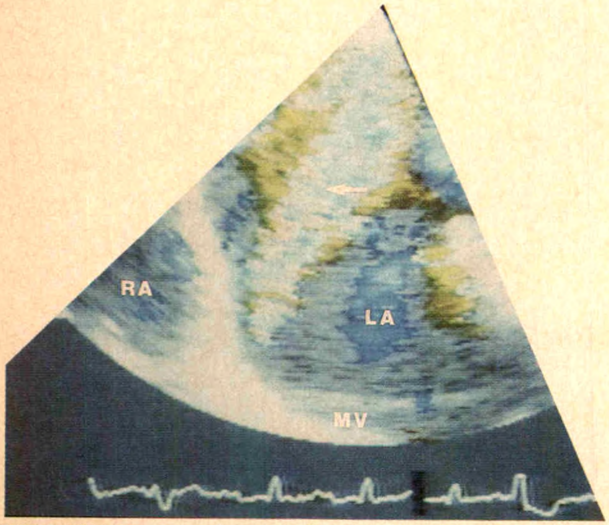

FIGURE 2. Transesophageal color flow Doppler of regurgitant St. Jude mitral valve (MV). Note that the "pathologic" paravalvular regurgitant jet *(arrow)* is eccentric in its origin, occupies >50% of the left atrial chamber, and demonstrates a marked degree of color flow reversal and mosaic feature. LA = left atrium; LV = left ventricle; RA = right atrium.

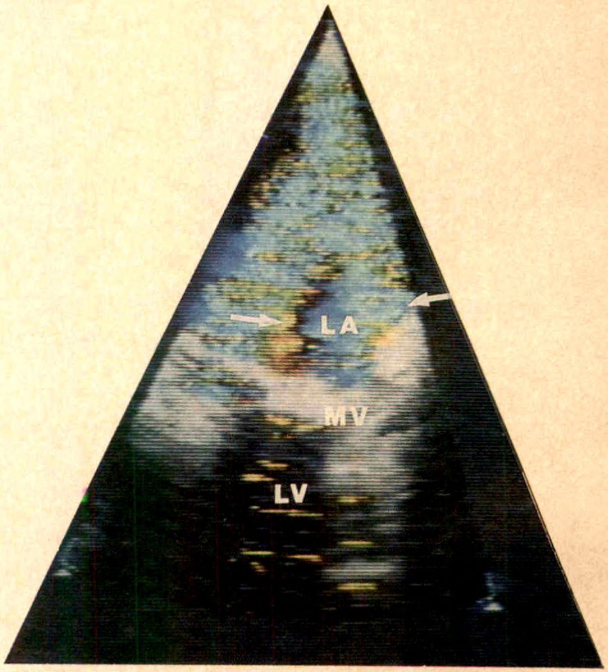

FIGURE 3. Transesophageal color flow Doppler of a patient with regurgitant St. Jude mitral valve (MV). Note that in this patient there are 2 pathologic regurgitant jets *(arrows)* filling the left atrium (LA). LV = left ventricle.

from the prosthetic disc masking the left ventricle and left atrium, respectively.

All 8 patients with regurgitant SJM prostheses had holosystolic color flow Doppler regurgitant jet occupying 50 to 90% of the left atrial chamber. The jet varied in length from 3 to 5 cm and in width from 3 to 4 cm. In all 8 patients, these jets were eccentric (paravalvular), shaped as a wide crescent or teardrop, with color flow reversal and mosaic pattern involving almost the entire jet (Figure 2). In 3 patients with previous endocarditis there were 2 sites of origin of the color flow regurgitant jet (Figure 3).

Transthoracic color flow Doppler using multiple acoustic windows in these 8 patients demonstrated either no regurgitation in 4 patients or only mild regurgitation (4 patients). It was not possible from transthoracic color flow Doppler to determine if the mild regurgitation seen in these 4 patients was physiologic or pathologic. At the time of surgery the site of valve regurgitation was paravalvular in all 5 instances.

Both transesophageal and transthoracic 2-dimensional echocardiograms were normal in 7 of 8 regurgitant valves. Vegetations or mass echoes were observed in 1 patient who had a small mobile mass at the valve sewing ring demonstrable by transesophageal but not by transthoracic 2-dimensional echocardiography. At the time of surgery this patient had vegetations and dehiscence of the valve at its sewing ring.

Transesophageal color flow Doppler reveals "physiologic" holosystolic mitral regurgitation in all patients with normal functioning SJM prostheses in the mitral valve position. Variations in the extent and turbulence of physiologic mitral regurgitant jets during study may be explained by fluctuations in systolic blood pressure that alter the left ventricular to left atrial pressure gradient.

This study demonstrated that it is possible by transesophageal color flow Doppler to differentiate "physiologic" mitral regurgitation from pathologic regurgitation by the characteristics of the color flow regurgitant jet. All our patients with pathologic mitral regurgitation had a more extensive crescent- or teardrop-shaped jet, which was eccentric (paravalvular), with color flow reversal and mosaic pattern encompassing most of the regurgitant jet. This study indicates that transesophageal color flow Doppler is a highly sensitive indicator of SJM prosthetic regurgitation. Therefore, we recommend this test in every symptomatic patient in whom this entity is suspected, even if transthoracic color flow Doppler is normal.

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Transesophageal Color Flow Doppler and Echocardiographic Features Of Normal and Regurgitant St. Jude Medical Prostheses in the Aortic Valve Position

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Transthoracic echocardiography and color flow Doppler have been shown to be of value in evaluating regurgitant St. Jude Medical (SJM) prostheses in the aortic valve position.[1] Transesophageal echocardiography and color flow Doppler show promise in evaluating normal functioning and regurgitant SJM mitral valves.[2,3] Recently transesophageal imaging has been shown to be superior to the transthoracic approach in demonstrating prosthetic valve vegetations.[4] This report describes our transesophageal ultrasound experience with 18 normal functioning, 2 regurgitant and 1 infected SJM prostheses in the aortic valve position.

Transthoracic and transesophageal echocardiography and color flow Doppler studies were performed in 21 patients with SJM prostheses in the aortic position. At the time of the transesophageal study, the valves had been in place from 1 day to 37 months (mean 10 months). Of the 21 transesophageal valve studies, 18 appeared normal and 2 had features of valve regurgitation and 1 was infected. All 3 abnormal valves resulted from bacterial endocarditis. Valve regurgitation and infection was substantiated by valve replacement surgery in 2 patients. The prosthetic valve replacement surgery was performed within 7 days of transesophageal study.

Transthoracic and transesophageal echocardiography and color flow Doppler studies were performed

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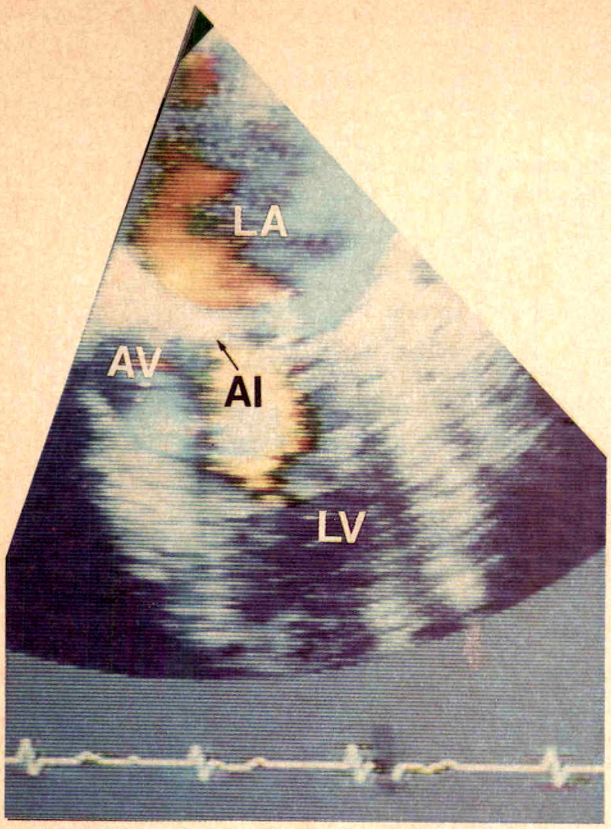

FIGURE 1. Transesophageal color flow Doppler of a patient with moderate paravalvular aortic insufficiency. Note the origin of the jet is eccentric (*arrow*). AI = aortic insufficiency; AV = aortic valve; LA = left atrium; LV = left ventricle.

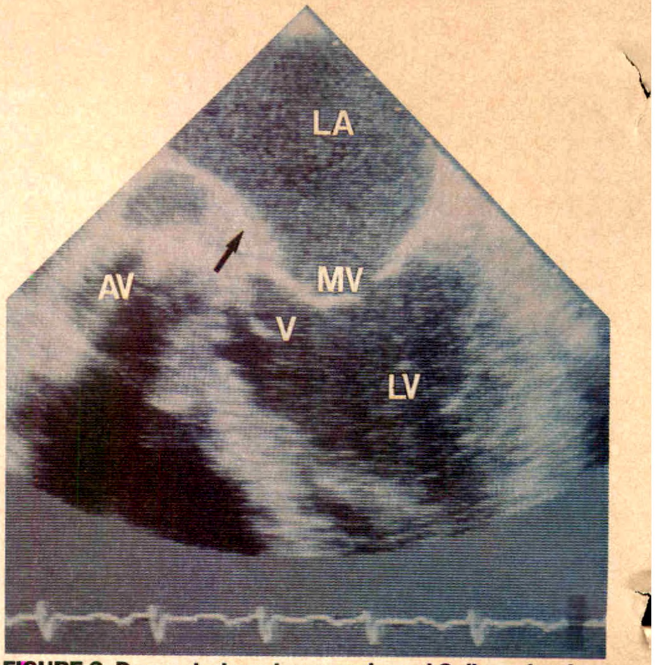

FIGURE 2. Demonstrates a transesophageal 2-dimensional echocardiogram of a patient with infected St. Jude aortic valve (AV). Note vegetations (V) protruding in the left ventricle (LV) outflow tract and aortic wall abscess (*arrow*). LA = left atrium; MV = mitral valve; V = vegetations.

within 8 days of each other. The transesophageal ultrasound was performed by previously described techniques[5] using a 5-MHz phased-array imaging transducer (Hewlett-Packard model 21352-A). In 7 patients the transesophageal study was performed in the operating room, whereas in 14 others the tests were performed on awake patients. The color flow gain and reject settings were adjusted to just below the level at which background noise was seen.

All valves were evaluated by color flow Doppler for the presence or absence of valve regurgitation. The color flow Doppler regurgitant jet length, width, duration, location, shape and color characteristics were evaluated by playing back the video tape and frame-by-frame analysis. The aortic valve regurgitation by transthoracic and transesophageal color flow Doppler was semiquantitated by relating the height/width of the regurgitant jet to the left ventricular outflow tract.[6]

Transesophageal color flow Doppler in all 18 normal functioning SJM prostheses did not demonstrate any regurgitation. In only 1 of 18 patients, a single narrow jet of aortic regurgitation was demonstrated by transthoracic, but not by transesophageal, study. Echocardiographic 2-dimensional (2-D) images by both transesophageal and transthoracic approach revealed multiple echoes emanating from the disc.

In 2 patients with regurgitant SJM prostheses the jet was directed toward the left ventricular outflow tract during diastole (Figure 1). Both transesophageal and transthoracic color flow Doppler graded the regurgitation to be moderate in 1 and severe in another instance. The patient with severe SJM aortic valve regurgitation also had diastolic protrusion of the valve apparatus into the left ventricular outflow tract demonstrable by 2-D echocardiography. This patient had bacterial endocarditis and demonstrated partial dehiscence of the valve at its suture ring during surgery.

One patient with infected SJM prostheses but no regurgitant murmur had vegetations protruding in the left ventricular outflow tract and aortic root abscess (Figure 2) by transesophageal 2-D study, and mild aortic regurgitation by color flow Doppler. These features were confirmed during surgery. Transthoracic 2-D imaging failed to demonstrate the vegetations and aortic root abscess but did detect mild aortic regurgitation.

The results of our studies indicate that there does not appear to be any advantage of transesophageal to transthoracic color flow Doppler in evaluating physiologic or pathologic degree of SJM aortic valve regurgitation. This is partly because aortic SJM prosthesis is well suited to analysis by transthoracic echocardiography.[1] The color flow jet from aortic regurgitation comes directly at a transducer positioned at the apex or is directly below a transducer positioned at the left sternal border. Furthermore, the Doppler sound beam does not have to traverse the mechanical prosthesis from this approach.

Transesophageal 2-D echocardiography, however, was clearly superior to the transthoracic imaging in diagnosing SJM aortic valve vegetations and aortic root abscesses.

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Comparison of Clinical Features in Patients ≥60 Years of Age to Those ≤40 Years of Age with Hypertrophic Cardiomyopathy

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The diagnosis of hypertrophic cardiomyopathy (HC) is based on the demonstration of unexplained left ventricular hypertrophy and may follow the development of symptoms or represent an incidental finding during routine examination from infancy to the grave. The natural history is characterized by a slow progression of symptoms and a high incidence of sudden death.[1] In most clinical and prognostic studies, the majority of patients are aged 18 to 60.[2-4] Though diagnosis and morphological features of HC in the elderly have been emphasized recently, detailed clinical features and left ventricular function have not been reported.[5-9] We compared clinical features in elderly patients with those in the young and also evaluated the influence of age on indexes of systolic and diastolic function derived from equilibrium radionuclide angiography in HC.

One hundred sixty-one consecutive patients with HC who underwent radionuclide angiography were studied. They were aged 8 to 78 years (mean 42); 23 were ≥60 years, 63 were >40 and <60 and the remaining 75 were ≤40 years; 90 were men and 71 women. The diagnosis of HC was based on the echocardiographic demonstration of unexplained left ventricular hypertrophy.[10] All patients had systolic and diastolic blood pressure <140 and <90 mm Hg, respectively. The pattern of left ventricular hypertrophy was asymmetric septal in 117 (73%), concentric in 31 (19%) and distal in 13 (8%) according to echocardiographic criteria described previously.[10] Thirty-five patients (22%) had systolic anterior motion of the mitral valve with septal contact. Coronary angiography was performed when patients ≥40 years old had exertional chest pain or an abnormal exercise test, or both. Eighteen of 23 elderly patients underwent coronary angiography; 2 had significant coronary artery disease. Forty-eight-hour ambulatory electrocardiography was performed at initial evaluation in all patients while not receiving cardioactive medication. Paroxysmal

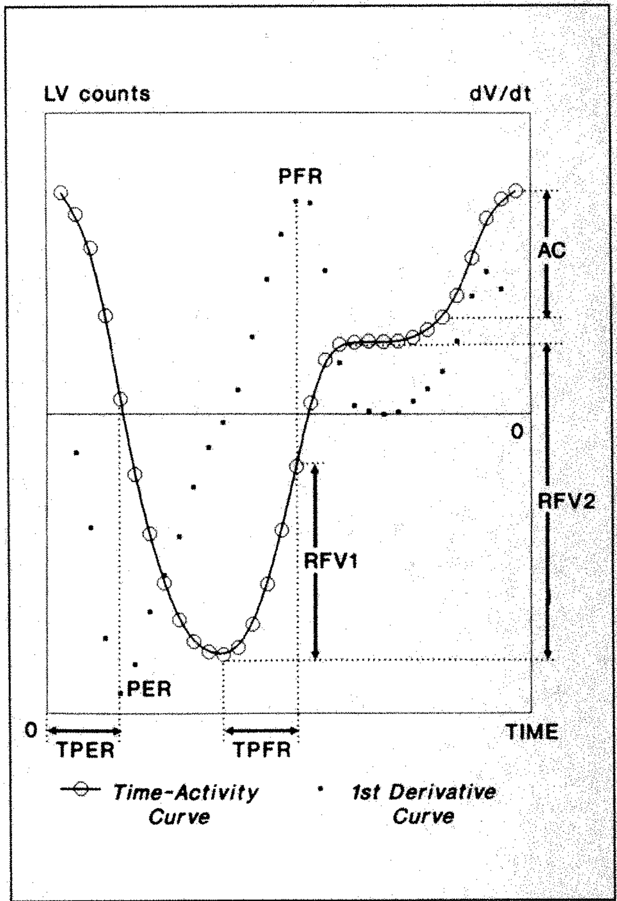

FIGURE 1. Calculation of peak rates of ejection and filling, time intervals and relative filling volumes from the radionuclide time-activity curve and its first derivative curve. Peak ejection and filling rates were normalized to end-diastolic counts and expressed as change from end-diastolic volumes/s (edv/s). Time to peak ejection rate (TPER) was defined as the interval from R-wave to the point of peak ejection and time to peak filling rate (TPFR) as that from end-systole (*minimum of the curve*) to the point of peak filling. Relative filling volume by peak filling rate (RFV1), relative filling volume during the rapid filling period (RFV2) and atrial contribution (AC) were defined as proportional filling volume at each point and were normalized to end-diastolic counts. LV = left ventricle; PER = peak ejection rate; PFR = peak filling rate.

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TABLE I Comparison of Clinical Features in Elderly and Young Patients with HC

	Elderly (n = 23) No. (%)	Young (n = 75) No. (%)	p Value
Age at diagnosis (years)	61 ± 7	21 ± 9	
Age at the study (years)	65 ± 5	26 ± 8	
Duration of symptoms before diagnosis (years)	2.1 ± 2.0	2.0 ± 6.7	NS
Family history			
None	20 (87)	31 (41)	0.0006*
HC	2 (9)	17 (23)	
HC + sudden death	1 (4)	27 (36)	
Clinical symptoms			
Angina			
None	13 (57)	50 (66)	NS
Atypical	1 (4)	5 (7)	
Exertional	7 (30)	14 (19)	
Exertional + atypical	2 (9)	6 (8)	
Dyspnea			
I	12 (52)	47 (63)	NS
II	8 (35)	22 (29)	
III + IV	3 (13)	6 (8)	
Syncope			
None	20 (87)	56 (75)	NS
Presyncope	1 (4)	6 (8)	
Syncope	2 (9)	13 (17)	

* P value for no family history versus that of HC and that of HC + sudden death; dyspnea was classified by New York Heart Association functional class.

HC = hypertrophic cardiomyopathy; NS = not significant.

TABLE II Radionuclide Indexes of Systolic and Diastolic Function: Elderly Versus Young Patients

	Elderly (n = 23)	Young (n = 75)	p Value
EF (%)	79 ± 12	77 ± 11	NS
PER (edv/s)	4.2 ± 1.0	4.2 ± 1.0	NS
TPER (edv/s)	181 ± 22	175 ± 33	NS
PFR (edv/s)	3.1 ± 1.1	3.6 ± 1.0	0.08
TPFR (ms)	182 ± 56	192 ± 45	NS
RFV_1 (%)	38 ± 15	42 ± 12	NS
RFV_2 (%) (n = 84)	71 ± 14	79 ± 9	<0.025
AC (%) (n = 84)	26 ± 14	18 ± 10	<0.025

AC = atrial contribution; edv = end-diastolic volume; EF = ejection fraction; NS = not significant; PER = peak ejection rate; PFR = peak filling rate; RFV_1 = relative filling volume by peak filling rate; RFV_2 = relative filling volume during the rapid filling period; TPER = time to peak ejection rate; TPFR = time to peak filling rate.

TABLE III Correlations Between Age and Radionuclide Indexes of Systolic and Diastolic Function in 161 Patients with HC

	R	p Value
EF	−0.028	NS
PER	−0.108	NS
TPER	0.126	NS
PFR	−0.243	<0.005
TPFR	−0.136	NS
RFV_1	−0.254	<0.0025
RFV_2 (n = 140)	−0.316	<0.0005
AC (n = 140)	0.289	<0.0005
AC/RFV_2 (n = 140)	0.267	<0.0025

Abbreviations as in Tables I and II.

supraventricular tachycardia was defined as ≥3 consecutive atrial premature complexes at a mean rate of >120 beats/min and nonsustained ventricular tachycardia was defined as ≥3 consecutive ventricular premature complexes at a mean rate of >120 beats/min.

All patients were in sinus rhythm at the time of radionuclide study; patients with moderate-to-severe mitral regurgitation were excluded. The examination was performed in 73 while not receiving cardiac medication and at least 5 half-lives after the cessation of β blockers or verapamil in 53. Thirty-five patients were receiving amiodarone at the time of the study; 32 of them were aged <60 years and the remaining 3 were aged 60 or older.

Left ventricular systolic and diastolic function were assessed by R-wave gated equilibrium radionuclide angiography acquired in list mode.[11-13] All studies were performed at rest in the supine position; cuff blood pressure and heart rate were recorded after 10 to 15 minutes of rest before each study. After labeling of red blood cells in vivo using 15 mCi of technetium-99m,[11] images were acquired using a large field-of-view rotating gamma camera (General Electric Maxi 400T) and a medium sensitivity parallel hole collimator oriented in a 45° left anterior oblique projection with caudal tilt. Data were acquired from 600 to 900 consecutive cycles and stored in the computer (A2, Medical Data Systems) for subsequent analysis. An RR interval histogram was constructed and complexes falling outside an operator-selected range (± 10% from the mean RR interval) were rejected. A background-corrected composite left ventricular time-activity curve was then generated at a frame rate of 10 to 25 ms/frame by combined forward and reverse gating from the R wave.[12]

A standard count-based method was used for calculation of left ventricular ejection fraction.[12] Atrial contribution and relative filling volume during the rapid filling period were calculated automatically with use of the second derivative curve and were successfully measured in 140 (87%).[13] The remaining 5 indexes of systolic and diastolic function were derived as previously described (Figure 1).[12,13]

Results are expressed as mean ± 1 standard deviation. A Student t test was used to compare the means of the continuous variables and contingency tables were analyzed using a chi-square test. Correlations between age and radionuclide indexes were also calculated. The computations were performed using the SPSS-PC + computer program.

Clinical features in 23 elderly patients with HC aged 60 years or older are summarized in Table I. The mean age was 65 years; 10 were men and 13 women. In 12 of the elderly patients the study was performed at <1 year from diagnosis and it was done 1 to 16 years (mean 9) later in the remaining 11. There were no differences in duration of symptoms before diagnosis or time from diagnosis to the study between the elderly and young patients aged ≤40 years. Though family history of HC was less common in the elderly, the incidence of dyspnea, syncope and chest pain was not different when compared *with young patients (Table I). During follow-up of 3.8 ± 1.8 years, 3 elderly patients had disease-related mortality; 2 died suddenly and another died in cardiac failure after recurrent myocardial infarction.*

The pattern of left ventricular hypertrophy was concentric rather than asymmetric septal in more of the elderly (asymmetric septal 52, concentric 35, apical 13% in the elderly vs asymmetric septal 75, concentric 20, apical 5% in the young; $p = 0.11$). Maximal left ventricular wall thickness was less (20 ± 5 vs 23 ± 7 mm; $p = 0.07$) and left atrial dimension was greater (42 ± 9 vs 37 ± 7 mm; $p < 0.05$) in the elderly compared with the young. There was no difference between the groups in left ventricular end-diastolic dimension (42 ± 5 vs 42 ± 5 mm; difference not significant), left ventricular end-systolic dimension (26 ± 3 vs 25 ± 4 mm; difference not significant) or the incidence of systolic anterior motion of the mitral valve (incomplete 30, complete 17% in the elderly vs incomplete 19, complete 27% in the young; difference not significant). Five of the elderly had calcification of the mitral anulus; only 1 of them had systolic anterior motion of the mitral valve and narrowing of the left ventricular outflow tract.[8]

Paroxysmal supraventricular tachycardia and frequent ventricular premature complexes (>250 beats/day) were more common in elderly patients than in the young (65 vs 24%; $p = 0.0007$) (26 vs 5%; $p < 0.005$). The incidence of nonsustained ventricular tachycardia, however, was similar in both groups (22 vs 13%; difference not significant).

Systolic indexes were similar in the elderly and the young (Table II). Five radionuclide indexes of diastolic function were measured: peak filling rate was reduced and atrial contribution was increased as a consequence of decreased relative filling volume during the rapid filling period in elderly patients while time to peak filling rate and relative filling volume by peak filling rate were similar in the young and the elderly (Table II). Twelve elderly patients who were studied at <1 year from diagnosis had higher ejection fraction (82 ± 10 vs 75 ± 13%; $p = 0.15$) and longer time to peak ejection rate (188 ± 21 vs 173 ± 22 ms; $p = 0.10$) compared with those who were studied at ≥1 year, though there were no differences in peak ejection rate and the 5 diastolic indexes. The relation of age and radionuclide indexes of systolic and diastolic function assessed in all 161 patients are summarized in Table III. Age was not related to systolic indexes, but there was a weak but significant correlation of age and all diastolic indexes except time to peak filling rate.

Cardiac function in HC is characterized by hyperdynamic systolic function and impaired diastolic performance.[1] This study revealed that clinical symptoms and indexes of systolic function were similar in elderly and young patients with HC, but that the elderly had more severe impairment of diastolic function. The elderly had slow and delayed early filling with greater dependence on atrial contribution for maintenance of stroke volume. In normal subjects, indexes of systolic function do not differ in the elderly versus the young.[14,15] In contrast, diastolic indexes are significantly impaired in the elderly: echo/Doppler measurement of mitral valve E-F slope, atrial filling fraction/contribution and the maximal flow velocity during the rapid filling period are significantly correlated with age ($r = -0.35$ to -0.56, 0.69 to 0.82), as are radionuclide measurements of peak filling rate ($r = -0.47$ to -0.82).[16–19] The similarity of systolic indexes in the young and the elderly, and the relation of age and indexes of diastolic function in HC is consistent with observations in normal subjects.[14–19] In HC the correlations of indexes of diastolic function with age were weaker than reported in normal subjects. This may relate to the variations in morphology and function that are recognized between patients with HC. We speculate that serial data collected prospectively would be more likely to show stronger correlation with age and evidence of progressive deterioration in diastolic function.

The elderly also had increased left atrial dimension and more episodes of paroxysmal supraventricular tachycardia. The combination of an increased incidence of supraventricular arrhythmia and increased atrial contribution places elderly patients with HC at particular risk of acute hemodynamic deterioration as well as risk of embolic complications. The detection of nonsustained ventricular tachycardia during electrocardiographic monitoring is useful in the identification of high-risk adults with HC.[20] The elderly with HC have survived the decades of greatest mortality. Electrocardiographic monitoring, however, should be particularly valuable in this subset as identification and treatment of those with supraventricular arrhythmia may prevent hemodynamic or embolic complications, or both.

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Obstruction of Systemic Pulmonary Arterial Shunts by Diagnostic Cardiac Catheters

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Accurate assessment of pulmonary artery pressure and pulmonary vascular resistance are essential in children who may be candidates for Fontan's operation.[1,2] In many such children, pulmonary blood flow is supplied primarily or entirely by systemic pulmonary arterial shunts. Because such shunts are frequently <5 mm in diameter, we proposed that passage of diagnostic cardiac catheters across these structures could partially obstruct the shunts, resulting in artifactually low measured pulmonary artery pressure and calculated pulmonary vascular resistance. This hypothesis was tested in an artificial circulation model and confirmed by clinical observations.

The artificial circulation model is shown schematically in Figure 1. Pressure was generated by a constant pressure reservoir, and an electrically activated valve driven by a square-wave generator produced pulsatile flow at 105 cycles/min. Flexible tubing (15 mm in diameter) was used for the model aorta and pulmonary artery. The system was filled with a sucrose solution adjusted to 4 cP relative viscosity. Model pulmonary arterial flow was provided by interchangeable glass tubes acting as systemic pulmonary arterial shunts. The shunts were 6-cm-long with a 5-mm internal diameter, which abruptly tapered to 2, 2.5, 3 or 4 mm at the distal (model pulmonary arterial) end. Ports for pressure measurement were placed in the model aorta and pulmonary artery. A third catheter insertion port was placed in the model aorta opposite the proximal end of the shunt for shunt catheterization. Screw clamps were placed at the ends of the model aorta and pulmonary artery to provide adjustable resistances, and effluent from both tubes was collected in a second constant pressure chamber, the height of which was chosen as the zero pressure level.

For each of the 4 shunt sizes, data were collected before shunt catheterization (baseline conditions), during shunt catheterization with 7Fr, 6Fr, and 5Fr multipurpose catheters (C.R. Bard) and with a 0.035-inch guidewire (used to roughly model the 2Fr micromanometer-tipped catheter used in the clinical observations), and after termination of shunt catheterization. Data collected consisted of flow rate and phasic and mean pressure in both the model pulmonary artery and aorta. Pressures were measured using micromanometer-tipped catheters (Millar Instruments, Houston, Texas) and recorded on a Gilson N-2 recorder. Flow rates were determined by timed effluent collections into graduated cylinders. Model pulmonary resistance and ratio of pulmonary to aortic effluent flow (QP/QS) were calculated in the usual fashion. Variance of all values obtained before

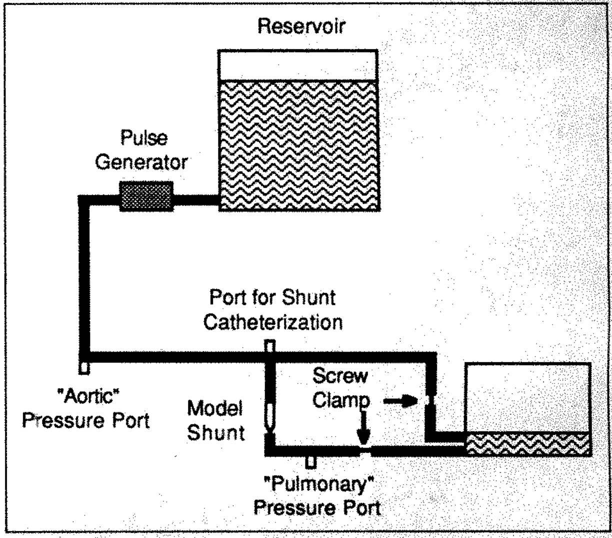

FIGURE 1. Diagram of artificial circulation model. The apparatus models single ventricle with shunt-dependent pulmonary blood flow. Interchangeable model shunts are described in the text. Model atrial and aortic systolic pressures are held constant by the constant pressure reservoirs.

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TABLE I Catheter Obstruction of Model Systemic Pulmonary Arterial Shunts

Catheter Size	Mean PA Pressure				QP/QS				Apparent RP*			
Shunt size (mm)	2	2.5	3	4	2	2.5	3	4	2	2.5	3	4
7Fr	—	—	−57†	−17†	—	—	−76†	−29†	—	—	−59†	−14†
6Fr	—	−75†	−33†	−14†	—	−85†	−53†	−24†	—	−77†	−36†	−7†
5Fr	−82†	−48†	−19†	−10†	−87†	−61†	−38†	−13†	−81†	−48†	−22†	−2
0.035 inch	−23†	−5	−7	2	−26†	−15†	−4	−1	−18†	−10†	−4	3

* Apparent RP = model pulmonary resistance calculated from flow in the baseline state and pulmonary pressure during shunt catheterization.
† $p < 0.05$ vs. baseline.
All data expressed as percent change from baseline.
PA = model pulmonary artery; QP/QS = ratio of model pulmonary to aortic flow; RP = model pulmonary resistance.

shunt catheterization and on termination of shunt catheterization was used to calculate 95% confidence limits for measurements in the basal (no catheter within the shunt) state; values falling outside these limits were considered significantly different. Statistically significant changes of >20% from baseline were considered clinically significant.

Changes in model pulmonary artery mean pressure and QP/QS are listed in Table I. Statistically significant changes occurred with catheterization of all 4 shunts by 5Fr, 6Fr and 7Fr catheters. Except for catheterization of the 4-mm shunt by the 5Fr catheter, all changes in QP/QS were clinically significant, as were most changes in mean pressure. Changes in systolic and diastolic pressure of the model pulmonary artery were similar to changes in mean pressure. Model pulmonary resistance during shunt catheterization (calculated using simultaneous model pulmonary pressure and QP) did not differ from baseline resistance. During diagnostic cardiac catheterization in shunted patients who are potential candidates for Fontan's operation, pulmonary artery pressure is commonly determined by catheterization of systemic pulmonary arterial shunts, and pulmonary blood flow is determined while the shunt is not catheterized. Table I lists the differences between model pulmonary resistance calculated in this fashion (using shunt catheterization model pulmonary artery pressures and baseline model QP) and true model pulmonary resistance (using baseline model pulmonary artery pressures and QP). Clinically significant underestimation of model pulmonary resistance occurred with passage of the 5Fr, 6Fr and 7Fr catheters across the 2-, 2.5- and 3-mm shunts.

A clinical example in which a systemic pulmonary arterial shunt is obstructed by a diagnostic cardiac catheter is shown in Figure 2. In this 2.5-year-old patient with pulmonary atresia and intact ventricular septum, a left Blalock-Taussig shunt was catheterized using a 5Fr multipurpose catheter through which a 2Fr (0.028-inch) micromanometer-tipped catheter (Millar Instruments) was passed into the pulmonary artery. Pressure was recorded from the micromanometer as the multipurpose catheter was withdrawn into the aorta. Mean pulmonary artery pressure was 80% higher when the shunt was not obstructed by the 5Fr catheter. Catheter passage across larger shunts in several other patients has caused smaller changes in pulmonary artery pressure, but aortic and pulmonary arterial oxygen saturations decreased by 5 to

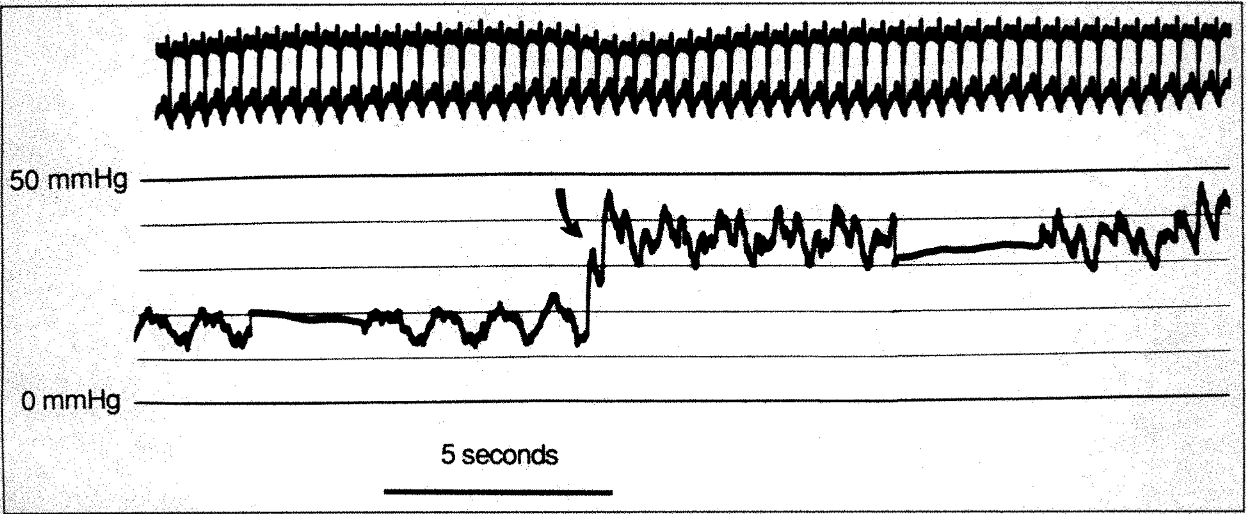

FIGURE 2. Clinical example of a systemic pulmonary arterial shunt obstructed by catheterization. The patient is a 2.5-year-old child with pulmonary atresia and intact ventricular septum in whom a left Blalock-Taussig shunt was constructed shortly after birth. The shunt has been catheterized by a 5Fr multipurpose catheter, and pressure is recorded from a 2Fr (0.028-inch) micromanometer-tipped catheter that has been passed through the 5Fr catheter into the pulmonary artery. Note the pronounced respiratory contribution to pulmonary artery pressure. At the point marked by the *arrow*, the 5Fr catheter is withdrawn into the aorta, leaving the 2Fr micromanometer catheter in the pulmonary artery. Mean pulmonary artery pressure increases from 19 to 34 mm Hg, and apparent pulmonary vascular resistance index increases from 1.7 to 4.2 U · m^2.

6 percentage points, indicating significant reductions in pulmonary blood flow.

Our observations indicate that systemic pulmonary arterial shunts can be obstructed readily by diagnostic cardiac catheters, resulting in underestimation of pulmonary artery pressure and pulmonary vascular resistance (Table I). Similar obstruction of severely stenotic aortic valves by diagnostic cardiac catheters has been reported in adults.[3] In the past, there has been no reliable way to confirm true pulmonary arterial pressure in patients dependent upon systemic pulmonary arterial shunts for pulmonary blood flow. The 2Fr micromanometer-tipped catheter potentially solves this problem, because the slightly larger 0.035-inch guidewire did not significantly alter pressure or flow in our model circulation. We recommend using the 2Fr micromanometer-tipped catheter for pulmonary artery pressure recording whenever accuracy is of clinical importance and the potential exists for catheter obstruction of a systemic pulmonary arterial shunt, pulmonary artery banding site or similar structure.

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Beta Adrenoceptors and m-Cholinoceptors in Myocardium of Hearts with Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy Removed at Cardiac Transplantation

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Myocardial force of contraction is regulated by receptors of the autonomic nervous system that are coupled either in a stimulatory or inhibitory way to the adenylate cyclase.[1] In the myocardium of patients with heart failure, there is a down-regulation of cardiac β adrenoceptors[2] with a reduction of the positive inotropic effects of β-adrenoceptor agonists and phosphodiesterase inhibitors.[3] However, little is known about inhibitory receptors such as muscarinic M_2-receptors, which couple to the inhibitory-guanine-nucleotide binding protein G_i and reduce force of contraction in the presence of β-adrenoceptor stimulation.[4] Since G_i has been reported to be increased in the failing human myocardium,[5,6] it is not unreasonable that these receptors could be coregulated with G_i. This would result in increased effects mediated by inhibitory M_2-receptor, which would contribute to the reduced response to cyclic adenosine monophosphate (cAMP)-dependent positive inotropic agents. Therefore, the number of myocardial β adrenoceptors and m-cholinoceptors were studied with radioligand binding techniques in explanted human hearts from patients undergoing cardiac transplantation because of severe heart failure (dilated cardiomyopathy, coronary heart disease) and in nonfailing donor hearts that could not be transplanted for technical reasons. The density and antagonist affinity of both β adrenoceptors and m-cholinoceptors were studied in the very same hearts and were correlated to the hemodynamic data obtained from patients before the operations.

The experiments were performed in 21 explanted hearts, which were obtained during cardiac transplantation. Eight patients had dilated cardiomyopathy (mean age 44 years, range 21 to 56) and 8 patients were transplanted for severe coronary heart disease (mean age 46 years, range 23 to 59). Five hearts from patients without echocardiographic evidence of heart failure were also studied (mean age 25 years, range 22 to 31). These hearts could not be transplanted for technical reasons. Tissue procurement was the same in all groups. Hearts were immediately delivered to the laboratory in ice-cold cardioplegic solution, frozen in liquid nitrogen and stored at −80°C. Freezing, storage and thawing procedures did not alter the results. From each heart, isolated electrically driven papillary muscles were prepared and force of contraction was measured. Developed basal tension and the increase in force of contraction after an elevation of the extracellular calcium ion concentration was similar in all groups (not shown) indicating that viable heart muscle was studied in all conditions.

Myocardial β adrenoceptors and muscarinic M_2-receptors were studied using the antagonist radiolabeled ligand ^{3}H-CGP 12.177 (^{3}H (−)-4-(3-t-butylamino-2-hydroxy-propoxy)-(5,7−^{3}H)-benzimida zol-2-one, 0.05 to 8 nmol/liter) and ^{3}H-QNB (^{3}H-quinuclidinylbencilate-(R)-benzilic-4,4-^{3}H(N), 0.05 to 3 nmol/liter), respectively. Cardiac glycoside receptors were studied with ^{3}H-ouabain according to Erdmann and Schoner.[7] Density (β_{max}) and antagonist affinity (k_D) were studied in the very same heart. Nonspecific binding was determined with 3 μmol/liter (−)propranolol for β adrenoceptors and 1 μmol/liter atropine for m-cholinoceptors, respectively. Density of muscarinic M_2-receptors and β adrenoceptors was related to mg membrane protein and to the number of ^{3}H-ouabain binding sites. There was no difference between binding of ^{3}H-ouabain to myocardial membranes in failing and nonfailing myocardium, indicating that the yield of myocardial membranes was similar in each group. Experimental details of radioligand

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TABLE I Nonfailing and Failing Myocardium

						Beta-AR			m-CH		
						Beta$_{max}$		K_D	Beta$_{max}$		K_D
Diag	LVEDP	LVEDV	EF	CI	Score	fmol/mg pr	fmol/pmol	nmol/liter	fmol/mg pr	fmol/pmol	nmol/liter
Nonfailing myocardium											
NF	—	—	—	—	—	87	13.5	0.33	307	47.6	0.65
NF	—	—	—	—	—	95	14.3	0.41	260	39.3	0.70
NF	—	—	—	—	—	110	23.9	0.83	274	59.5	0.40
NF	—	—	—	—	—	106	13.9	0.45	289	38.0	0.31
NF	—	—	—	—	—	102	21.0	0.61	272	40.0	1.00
X ± SEM						100	17.4	0.52	275	44.3	0.58
						± 3.7	± 2.4	(0.33–0.83)	± 21	± 4.5	(0.27–1.25)
Failing myocardium											
DC	12	275	26	2.2	6	36	7.2	0.50	117	23.4	0.30
DC	36	196	15	1.5	9	56	10.9	0.26	206	40.1	0.61
DC	20	201	24	1.6	10	38	8.2	0.60	350	75.0	0.47
DC	41	532	14	1.9	13	30	6.9	1.09	159	37.0	0.58
DC	28	400	12	2.6	11	25	4.1	0.75	196	32.6	0.66
DC	38	365	10	1.4	13	28	4.0	0.50	96	37.9	0.49
DC	30	270	20	1.7	9	53	10.0	0.45	215	49.0	0.40
DC	26	284	16	2.9	8	21	5.1	0.65	285	40.1	0.50
CAD	20	195	37	2.8	7	66	13.0	0.72	405	55.0	0.40
CAD	40	184	29	2.7	8	30	5.8	0.70	269	52.3	0.50
CAD	38	210	20	2.1	9	35	10.0	0.45	190	55.0	0.30
CAD	20	148	31	1.5	11	30	7.5	0.75	191	33.7	0.28
CAD	22	225	52	3.1	11	39	7.4	0.86	175	33.0	0.41
CAD	23	202	21	1.7	10	30	6.0	0.63	127	30.9	0.37
CAD	31	194	35	1.7	10	35	7.0	0.61	149	36.3	0.87
CAD	40	230	29	2.7	9	45	8.2	0.61	239	43.6	0.39
X ± SEM	29	257	24.4	2.2	9.6	37	7.24	0.57	211	38	0.47
	± 2.3	± 25	± 2.7	± 0.15	± 0.48	± 3.0	± 0.6	(0.39–0.83)	± 22	± 3.6	(0.38–0.50)

Hemodynamic measurements in patients with nonfailing myocardium were not performed.

Beta-AR = β adrenoceptor; Beta$_{max}$ = receptor density in fmol/mg protein (fmol/mg prot) or fmol/pmol ^{3}H-ouabain bound (fmol/pmol); CAD = coronary artery disease; CI = cardiac index (liters/min/m^2); DC = dilated cardiomyopathy; Diag = diagnosis; EF = ejection fraction (%); K_D = equilibrium dissociation constant as a measure of antagonist affinity (nmol/liter); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEDV = left ventricular end-diastolic volume (ml); m-CH = m-cholinoceptors; NF = nonfailing; SEM = standard error of the mean.

binding experiments are described elsewhere.[8] The data obtained in the biochemical experiments were related to the hemodynamic measurements obtained in these patients. The data were obtained at cardiac catheterization before operation, as listed in Table I. The heart failure score was calculated for each patient, as indicated in the legend to Figure 1. Hemodynamic data and receptor densities of patients are listed in Table I.

The number of cardiac β adrenoceptors was reduced in patients who underwent cardiac transplantation compared with the number of β adrenoceptors in nonfailing myocardium. There was a good correlation between the reduction of the number of β adrenoceptors and the hemodynamic measurements in these patients as judged from an increasing heart failure score (Figure 1A). In contrast, there was no change in the number of m-cholinoceptors in nonfailing and failing myocardium (Table I). There was no correlation between the number of muscarinic M_2-receptors and the change in heart failure score in the patients studied (Figure 1B). The k_D values did not differ between the groups studied and did not correlate to the heart failure score (not shown). The data were similar when related to mg membrane protein or pmol ^{3}H-ouabain bound as marker for myocardial membranes.

In explanted failing human hearts, a number of biochemical alterations have been identified, such as a downregulation of β adrenoceptors,[2] decrease of isoprenaline-stimulated adenylate cyclase activity[5,6] and an increase of G_i,[5,6] while the stimulatory guanine-nucleotide binding protein (G_s) appeared to be unchanged.[6,7] However, data on inhibitory, G_i-coupled M_2-receptors in human heart failure are lacking. An increase of muscarinic M_2-receptors could contribute to the reduced response to cAMP-dependent positive inotropic agents,[2,3,6] whereas a decrease would result in unopposed β-adrenergic stimulation of the failing myocardium. In dogs, a decline of muscarinic M_2-receptors has been reported in pressure overload-induced heart failure due to aortic stenosis.[8] In contrast, the data of our study show that an increase or decrease of muscarinic M_2-receptors was not observed in the very same human failing hearts in which a significant decline (by 56%) of β adrenoceptors was measured. These findings indicate that the number of muscarinic M_2-receptors is unchanged in human heart failure and an increased number of muscarinic M_2-receptors does not contribute to the blunted response to cAMP-increasing positive inotropic agents. The divergent findings obtained in the failing dog heart[9] might be due to species differences or to the different underlying myocardial diseases, such as pressure overload in the dog and ischemic or dilated cardiomyopathy in humans. The consequences of these findings are that data relevant to human heart disease should be obtained in human myocardium and not in laboratory animal models with acquired cardiomyopa-

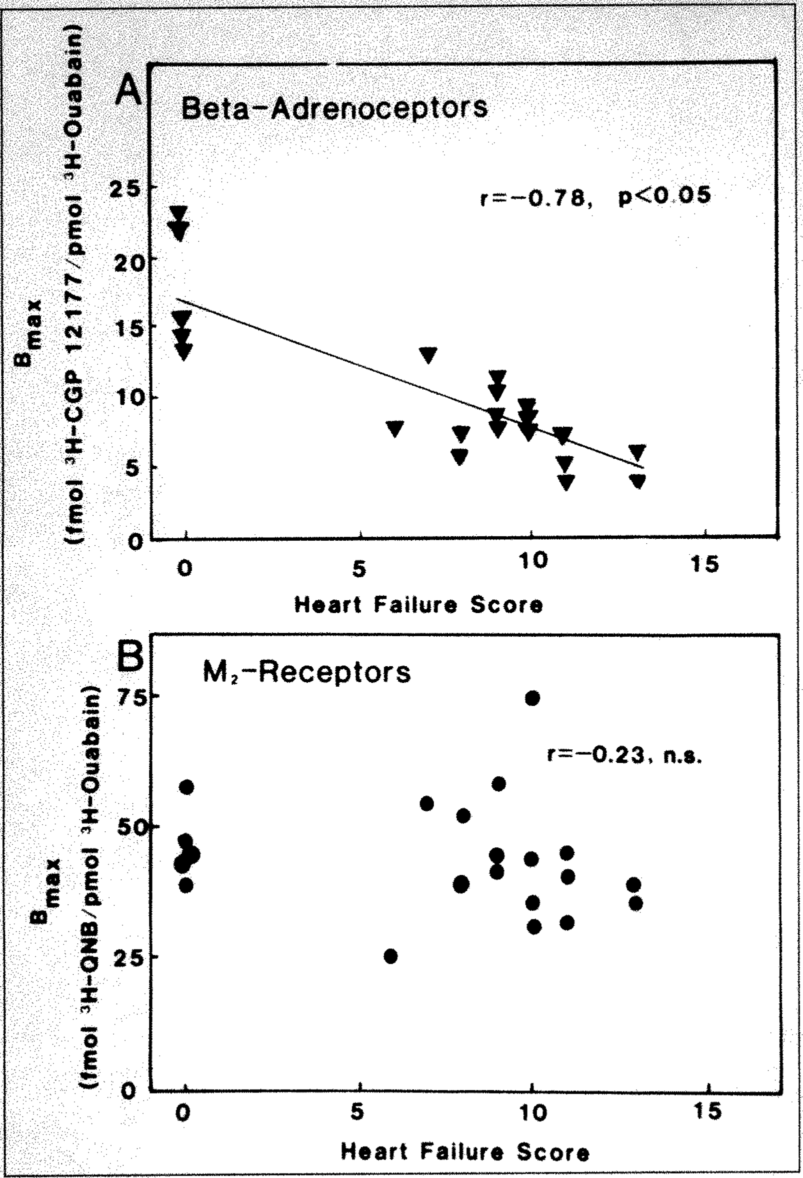

FIGURE 1. Correlation of the number (B_{max}) of β adrenoceptors *(A)* and the number of muscarinic M_2 receptors *(B)* to the heart failure score. Patients were classified according to a scoring system of points (p) evaluating the following hemodynamic data: (1) left ventricular end-diastolic pressure, which scored 0 p if <12 mm Hg, 1 p if 13 to 19 mm Hg, 2 p if 20 to 24 mm Hg and 3 p if >25 mm Hg; (2) left ventricular end-diastolic volume, which scored 0 p if <150 ml, 1 p if 150 to 200 ml and 3 p if >300 ml; and (3) cardiac index, which scored 0 p if >2.8 liters/min · m², 2 p if 2.0 to 2.8 liters/min · m², 4 p if <2.0 liters/min · m²; and (4) ejection fraction, which scored 0 p if >60%, 1 p if 40 to 60%, 2 p if 20 to 39% and 3 p if <20%. A significant correlation could only be obtained with β adrenoceptors. Note that the number of β adrenoceptors is related to pmol ^{3}H-ouabain bound as a marker of myocardial membrane proteins. n.s. = not significant.

thy, as results can be entirely different. The increase of G_i that has been observed in failing human hearts[5,6] might directly (independent of the M_2-receptor) attenuate adenylate cyclase activity, thereby impairing the functional response to cAMP-increasing positive inotropic agents.[3]

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Nongeometric Doppler Stroke Volume Determination is Limited by Aortic Size

Thomas R. Lloyd, MD, and Farshad Shirazi, MS

Noninvasive stroke volume determination by Doppler echocardiography has traditionally required estimation both of mean flow rate during ejection by Doppler methods and of flow area by cross-sectional or M-mode echocardiography.[1] Spodick and Koito[2] recently reported a method for estimating stroke volume from Doppler echocardiographic tracings alone, which they term nongeometric because no area measurement is used. Instead, mean left ventricular ejection rate is estimated from mean Doppler velocity and is then multiplied by Doppler ejection time to yield stroke volume. We reasoned that if there is a physiologic relation between ejection rate and Doppler velocity, truly independent of aortic size, the nongeometric method should also accurately estimate stroke volume in infants and children, who have a wide range of aortic size.

Doppler echocardiographic studies from 20 consecutive patients meeting the criteria below were examined. Criteria for inclusion were recordings of pulsed Doppler velocity at the aortic anulus from the apical window and recordings of the aortic valve in the parasternal long-axis view suitable for measurement of aortic anulus diameter. Exclusion criteria were patient age ≥21 years, left ventricular outflow tract obstruction, abnormally small aortic diameter or congestive heart failure. Aortic anulus diameter was measured according to Roman et al,[3] and aortic cross-sectional area (cm^2) was calculated assuming a circular profile. Mean Doppler velocity during ejection (Vmean, in m/s) was measured by the method of Donnerstein and Marx[4] in 5 Doppler tracings from each patient, and Doppler ejection time(s) was measured by the method of Koito and Spodick[5] in the same tracings. Geometric stroke volume was calculated as the product of aortic cross-sectional area, ejection time and Vmean (converting Vmean to cm/s), and nongeometric stroke volume was calculated according to Spodick and Koito.[2] Mean values for geometric and nongeometric stroke volume were calculated for each patient.

Patient age ranged from birth to $10\frac{3}{12}$ years (median 3 months; 13 patients were <1 year old). Six of the infants were premature and 4 weighed <2 kg at the time of echocardiography. Aortic cross-sectional area ranged from 0.24 to 2.54 cm^2. Echocardiographic diagnoses included small ventricular septal defect in 3, atrial septal defect or patent foramen ovale in 3, patent ductus arteriosus in 2, pulmonary artery branch stenosis in 3, pulmonary stenosis in 1, pulmonary heart disease in 2 and normal hearts in 8 patients, including 2 who had previous surgical repair of congenital cardiac defects. Geometric and nongeometric stroke volumes are listed in Table I. Geometric stroke volume ranged from 2.3 to 63 ml (median 8.7), and was significantly smaller (p <0.0001, repeated measures analysis of variance) than nongeometric stroke volume (range 27 to 105 ml, median 66). The nongeometric method overestimated geometric stroke volume by 66 to 1,521%, or by 25 to 80 ml absolute volume. Geometric stroke volume showed much better correlation with age (r^2 = 0.908) and with aortic cross-sectional area (r^2 = 0.943) than with nongeometric stroke volume (r^2 = 0.538). Nongeometric stroke volume correlated poorly with age (r^2 = 0.376).

Nongeometric Doppler stroke volume substantially overestimated Doppler stroke volume calculated by traditional geometric methods. We used geometric Doppler stroke volume as the standard in our study rather than thermodilution as used by Spodick and Koito[2] because in our laboratory Doppler methods have agreed closely with the Fick method[1] and because thermodilution tends to be inaccurate at flow rates as low as seen in infants and children.[1] This study used the same values for Vmean and ejection time to calculate stroke volume by both methods, so influence of Doppler incidence angle would apply equally to both methods.

Examination of the theoretical basis of the nongeometric method readily explains the observed discrepancy in stroke volumes. The nongeometric method is based on

TABLE I Geometric and Nongeometric Stroke Volumes in 20 Infants and Children

Pt.	Age (yr)	Geometric SV (ml)	Nongeometric SV (ml)	Difference in SV (ml)	Difference in SV (%)
1	6.0	38	76	38	100
2	10.3	52	98	46	88
3	1.8	28	94	66	236
4	0.0	4.2	52	48	1138
5	0.5	13	66	53	408
6	0.0	8.5	60	51	606
7	7.7	63	105	42	67
8	0.0	8.5	61	52	618
9	0.1	6.1	86	80	1310
10	0.0	2.9	47	44	1521
11	1.1	18	72	54	300
12	0.3	8.1	80	72	888
13	0.2	8.7	48	39	452
14	0.3	9.5	60	50	532
15	0.0	4.5	30	25	567
16	0.1	2.3	27	25	1074
17	0.1	8.7	71	62	716
18	4.2	31	59	28	90
19	0.1	7.1	56	49	689
20	6.5	43	83	40	93
mean ± SD		18 ± 18	67 ± 21*	48 ± 15	574 ± 433

* $p < 0.05$ vs geometric stroke volume.
SD = standard deviation; SV = stroke volume.

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an observed relation[6] between mean left ventricular ejection rate (LVER, in ml/s) and Vmean, as shown in equation 1: LVER = 494 (Vmean) − 66. In the geometric method, left ventricular ejection rate is the quotient of stroke volume and ejection time, and stroke volume is the product of ejection time, aortic cross-sectional area (CSA), and 100 · Vmean (Vmean is multiplied by 100 to convert m/s to cm/s). Therefore, by the geometric method, ejection rate can be expressed as in equation 2: LVER = 100 · Vmean · CSA. Equations 1 and 2 can be combined and rearranged to solve for aortic cross-sectional area, producing equation 3: CSA = 4.94 − 0.66/Vmean. Obviously, this equation cannot correctly predict stroke volume if aortic cross-sectional area is more than 4.94 cm^2 (aortic valve diameter >2.5 cm). Over the range of Vmean reported in the studies describing and validating the nongeometric relation between LVER and Vmean, aortic diameter would vary from 1.84 to 2.34 cm, values well outside normal limits for the first decade of life.[7] Conversely, for the nongeometric method to predict accurately the CSA of a normal newborn, Vmean would have to be 0.14 m/s, a markedly low value.

We conclude that the nongeometric Doppler stroke volume determination method of Spodick and Koito[2] cannot be extended to infants and children. Indeed, our data indicate that a child's age or aortic diameter—without any Doppler information—is much more predictive of stroke volume than is the nongeometric method. We suggest that the success of this method in estimating left ventricular ejection rate and stroke volume[2,6] is primarily due to the relatively constant diameter of the normal adult aortic anulus (1.3 ± 0.1 cm/m^2, [3]). Within this range, using measured or assumed aortic size may not substantially alter accuracy of Doppler stroke volume, but for patients who fall outside the range a nongeometric method or measured aortic size must be used. Although Spodick and Koito[2] made no claim that their method could be extended beyond the adult population they studied, it is disappointing that their method fails in precisely those patients in whom a nongeometric method would be of greatest advantage.

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Quantification of Tricuspid Regurgitation by Doppler Color Flow Mapping After Cardiac Transplantation

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Color-coded Doppler echocardiography permits visualization of the spatial distribution of flow velocities produced by valvular regurgitation with a high sensitivity.[1] Doppler color flow mapping has been used for simple noninvasive assessment of the magnitude of aortic and mitral regurgitation, and a reasonable agreement between the angiographically estimated grade of aortic or mitral regurgitation and Doppler color flow variables has been reported.[1-3] Doppler color flow mapping is a sensitive and specific technique in detecting tricuspid regurgitation.[4] However, little is known about the assessment of the magnitude of tricuspid regurgitation by color Doppler flow imaging, probably because a reliable reference standard for the assessment of tricuspid regurgitation is lacking. Therefore, we compared various measurements derived from the color Doppler flow imaging with the tricuspid regurgitant fraction obtained by a double thermodilution technique. The study group consisted of cardiac transplant patients who are known to have a high incidence of tricuspid regurgitation without any other valve abnormalities.[5,6]

The study includes 40 patients (30 men, 10 women, mean age ± standard error 45 ± 2 years) who had undergone orthotopic cardiac transplantation for end-stage ischemic cardiomyopathy (n = 20), idiopathic dilated cardiomyopathy (n = 19) and idiopathic restrictive cardiomyopathy (n = 1). All patients underwent routine diagnostic cardiac catheterization 13 ± 2 months after cardiac transplantation including right-sided heart biopsies. Within 24 hours before or after cardiac catheterization, the patients were examined by Doppler echocardiography. At the time of cardiac catheterization, none of these patients had severe heart rejection as judged by biopsy specimen.

In addition to routine right and left heart biplane angiography and coronary angiography, all patients were studied by a double thermodilution technique in order to quantify tricuspid regurgitant fraction.[7] For this technique, 2 isosensitive Swan-Ganz thermodilution catheters (American Edwards) were placed into the right atrium and the pulmonary artery (Figure 1, top). Cold saline (8°C, 10 ml) was injected into the right ventricle

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TABLE I Correlation of Tricuspid Regurgitant Fraction Obtained by a Double Thermodilution Technique and Various Pressure Measurements Obtained by Right-Sided Cardiac Catheterization

Correlation of TRF with:	Linear Regression Equation	r	SEM	p
Mean right atrial pressure (mRAP)	(TRF%) = 1.2 (mRAP) + 5.6	0.54	17.6	0.0004
Right atrial *v* wave (RAv)	(TRF%) = 1.3 (RAv) + 0.02	0.64	15.9	0.0001
Systolic right ventricular pressure (RV)	(TRF%) = −0.9 (RV) + 12.3	0.10	20.7	NS
Mean pulmonary artery pressure (mPAP)	(TRF%) = −0.3 (mPAP) + 0.57	0.24	20.2	NS

The pressures obtained by right-sided cardiac catheterization are given in mm Hg; regression analysis using only patients with TRF ≥5% showed similar significant results.
SEM = standard error of the mean; TRF = tricuspid regurgitant fraction (%).

just beneath the tricuspid valve. The regurgitant fraction was calculated as the area ratio of dilution curves obtained simultaneously in the right atrium and pulmonary artery (Figure 1, bottom). At least 3 to 5 different measurements were averaged. For each measurement, the position of the tip of the thermodilution catheter in the right atrium was changed. A tricuspid regurgitation fraction (TRF) <5% was considered as artifical (cold transmission, no tricuspid regurgitation).

Two-dimensional and Doppler echocardiographic studies were performed with a Hewlett-Packard unit (2.5 MHz phased-array transducer) using standard techniques. The regurgitant jet was visualized by color Doppler in systole during inspiration hold. Different projections and angulations were repeated until maximal flow images could be achieved. Care was taken to use an optimal gain setting without appearance of signals outside the regurgitant flow or onto tissue (Figure 2). Each examination was performed using shallowest depth and narrowest sector angle in order to obtain maximal frame rate. From color Doppler flow images, maximal length and maximal area of the tricuspid signal were derived. The right atrial area was traced and the ratio maximal jet area to right atrium area was calculated. In 6 of 40 patients in whom the entire border of the right atrium could not be visualized, the missing regions were approximated by visual interpretation.

The TRF varied between 2 and 76% (<5% n = 14; 5 to 30% n = 12; >30% n = 14). The correlation between the regurgitant fraction and the hemodynamic variables obtained during right-sided cardiac catheterization are listed in Table I.

Table II summarizes the correlation of the TRF with the measurements derived from the color Doppler flow imaging. The highest correlation coefficient was obtained with the ratio maximal area of the tricuspid regurgitant signal to right atrium area (Figure 3). All 3 Doppler-derived variables showed a weak but significant correlation with the right atrial v *wave (maximal jet length: r = 0.61; maximal jet area: r = 0.65; ratio jet area to right atrial area: r = 0.69).*

This study shows that Doppler color flow mapping of the tricuspid regurgitant signal seems to be useful in estimating the magnitude of regurgitation as determined by a double thermodilution technique. Both the maximal length and the maximal area of the tricuspid regurgitant

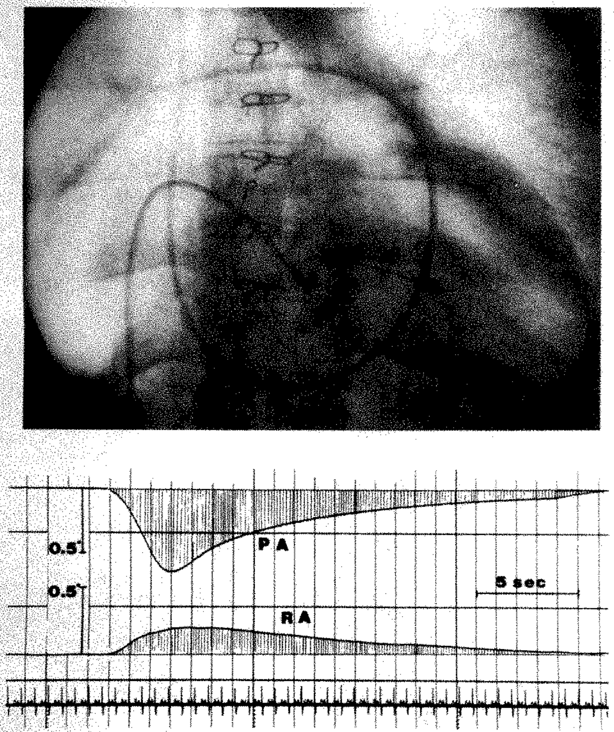

FIGURE 1. For the double thermodilution technique, 2 isosensitive Swan-Ganz catheters were placed in the right atrium and the pulmonary artery (PA) *(top)*. Cold saline was used as an indicator and was injected into the right ventricle. Tricuspid regurgitant fraction was calculated as the area ratio of dilution curves measured simultaneously in the right atrium (RA) and the pulmonary artery *(bottom)*. In this example, a tricuspid regurgitant fraction of 38% was calculated.

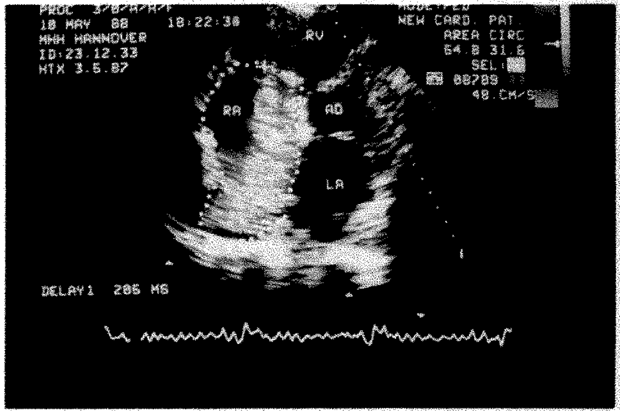

FIGURE 2. Color Doppler echocardiography in a patient with severe tricuspid regurgitation 1 year after successful cardiac transplantation; angulated parasternal short-axis view. Note the huge regurgitant jet in systole. The right atrium (RA) area is outlined. AO = aorta; LA = left atrium; RV = right ventricle.

TABLE II Correlation of Tricuspid Regurgitant Fraction Obtained by a Double Thermodilution Technique with Various Measurements Derived from Color Doppler Flow Imaging

Correlation of TRF with:	Linear Regression Equation	r	SEM	p
Maximal jet length (L cm)	(TRF%) = 6.9 (L) − 2.5	0.79	12.9	0.0001
Maximal jet area (A cm²)	(TRF%) = 2.6 (A) + 3.2	0.84	11.0	0.0001
Ratio jet to right atrium area (A/RA)	(TRF%) = 1.3 (A/RA) − 0.5	0.89	9.5	0.0001

Regression analysis using only patients with TRF ≥5% showed similar significant results.
SEM = standard error of the mean; TRF = tricuspid regurgitant fraction (%).

signal correlated with the regurgitant fraction, and the best correlation was found when the maximal jet area was related to right atrial area. Our results support the findings of Chopra et al,[8] who recently used Doppler color flow mapping to identify patients with severe tricuspid regurgitation as judged intraoperatively. They found that a ratio of maximal area of the tricuspid regurgitant signal to right atrial area ≥34% identifies patients with a high sensitivity who would require subsequent tricuspid valve repair. With use of our linear regression equation (Table II), this ratio of 34% represents a TRF of about 44%, which indeed corresponds to clinically significant tricuspid regurgitation.

Although we found a highly significant correlation between TRF and color Doppler-derived parameters, the complexity that actually determines the color-coded regurgitant signal should be kept in mind. Numerous studies showed that the spatial distribution of the regurgitant flow as assessed by color Doppler flow imaging is crucially dependent on flow velocities and therefore on regurgitant pressure rather than on regurgitant volume.[9] Furthermore, a variety of technical, physiologic and methodologic factors can influence the grading of regurgitation by color Doppler flow mapping, as has been stressed previously.[10] Furthermore, different pathogeneses of tricuspid regurgitation might influence the color flow signal (e.g., >1 tricuspid regurgitant jet, different right ventricular pressures, different size of right atrial chamber). Thus, these various factors that potentially influence tricuspid regurgitant signals like the signal of any other regurgitant lesion may limit the clinical application of this technique in calculating TRF, and the presented regression equations may vary between laboratories. However, despite all these technical considerations, a close correlation between Doppler color flow mapping and double thermodilution technique was possible in patients with tricuspid regurgitation. Because an increase in incidence and severity of tricuspid regurgitation has been reported in patients after cardiac transplantation,[6] Doppler color flow mapping might be a useful method for follow-up examinations in these patients.

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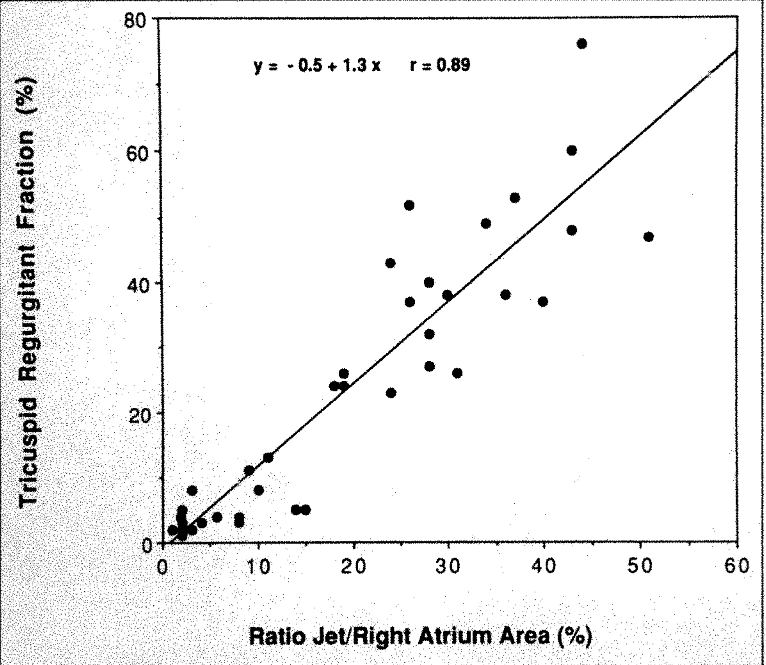

FIGURE 3. The ratio of area of the regurgitant jet across the tricuspid valve to the area of the right atrium (averaged from different orthogonal planes) was measured using color Doppler flow images and corresponding 2-dimensional echocardiograms, and was correlated with the tricuspid regurgitant fraction obtained by a double thermodilution technique. The regression equation for linear regression is given (n = 40 patients).

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Cyclic Adenosine Monophosphate Content of Endomyocardial Tissue Obtained by Biopsy in Cyclosporine Immunosuppressed Human Cardiac Transplant Recipients

Randall C. Starling, MD, Donald F. Hammer, MD, and Donald V. Unverferth, MD*,
with the technical assistance of Stephan Wetzal and Robert E. Kelley

Our laboratory has previously reported the myocardial cyclic adenosine monophosphate (AMP) content in normal humans and patients with cardiomyopathy.[1] Concentric left ventricular hypertrophy and hemodynamic abnormalities suggestive of diastolic dysfunction have been observed in the transplanted heart.[2,3] The etiology of the diastolic dysfunction is unknown. Cyclic AMP content may increase in response to depletion of myocardial energy stores and may serve as a stimulus for protein synthesis and ventricular hypertrophy. Cyclosporine, a commonly used immunosuppressive agent, has been shown to have an affinity for the calcium regulatory protein calmodulin.[4] Calmodulin in vitro can stimulate adenylate cyclase, thereby potentially increasing cyclic AMP, and, in addition, can stimulate phosphodiesterase, hence theoretically decreasing cyclic AMP levels. This investigation measures the myocardial cyclic AMP con-

TABLE I Clinical Features of Patient Groups

Group	Patients Men/Women	Age (yrs)	Blood Pressure Systolic (mm Hg)	Blood Pressure Diastolic (mm Hg)	RA (mm Hg)	PAW or LVEDP (mm Hg)	LVEF (%)
Normal subjects	2/2	50 ± 11	120 ± 9	69 ± 12	3 ± 1	10 ± 3	60 ± 9
DCM	6/4	52 ± 11	133 ± 20	78 ± 10	8 ± 7	23 ± 11	35 ± 12
Transplant	8/5	46 ± 8	133 ± 16	99 ± 9	6 ± 4	11 ± 5	57 ± 11

Data are mean ± standard deviation.
BP = blood pressure; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; PAW/LVEDP = pulmonary artery wedge or left ventricular end-diastolic pressure; RA = mean right atrial pressure.

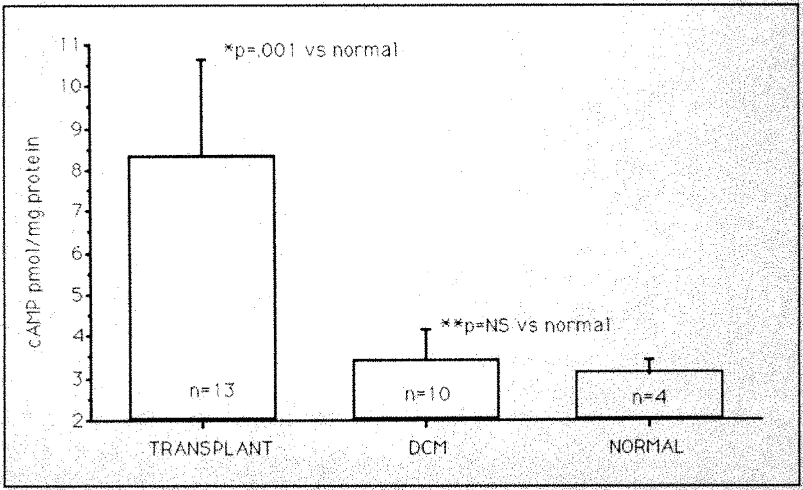

FIGURE 1. Cyclic AMP pmol/mg protein myocardial content expressed as mean (±) standard deviation for cardiac transplant recipients, dilated cardiomyopathy (DCM) and normal subjects. cAMP = cyclic adenosine monophosphate.

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tent in cyclosporine-treated cardiac transplant recipients. We hypothesized that the hemodynamic and anatomic (hypertrophy) abnormalities observed in the transplanted heart may be related to abnormalities in myocardial cyclic AMP content.

The study population comprised 13 cardiac transplant recipients receiving immunosuppression consisting of cyclosporine, azathioprine and prednisone. These patients were compared with 4 normal subjects and 10 patients with dilated cardiomyopathy previously reported.[1] The 4 "normal" patients had chest pain and angiographically normal coronary arteries. The patient groups and their clinical features are listed in Table I. All 13 cardiac transplant recipients showed no evidence of allograft rejection in endomyocardial biopsies performed at the time parallel samples for cyclic AMP measurement were obtained. Ejection fractions were obtained by contrast angiographic assessment or radionuclide angiography. Hemodynamic measurements were obtained at the time the endomyocardial biopsy was performed. The length of time from transplantation until acquisition of the biopsy sample ranged from 34 to 651 days (mean 340 ± 241).

Using sterile technique, the right internal jugular vein was cannulated and 2 endomyocardial specimens were obtained using a 54 cm, 2.4 mm cup size Cordis bioptome. Right ventricular endomyocardial biopsies were placed in liquid nitrogen within 10 seconds. Cyclic AMP was analyzed by radioimmunoassay and the protein was determined by the Lowry method as previously described.[1] The groups were compared by 1-factor analysis of variance. The study was approved by the Institutional Review Board for Human Subjects and each patient gave informed written consent.

In Figure 1, the mean ± standard deviation myocardial cyclic AMP content for each group is shown. There is a significant elevation in myocardial cyclic AMP content (8.3 pmol/mg protein) in cardiac transplant recipients compared with that of normal subjects (3.1 pmol/mg) and the cardiomyopathy group (3.4 pmol/mg). No correlation was shown between cyclic AMP and either preload (pulmonary artery wedge pressure or left ventricular end-diastolic pressure) or left ventricular ejection fraction. No correlation was present between length of time from transplantation until sampling and the cyclic AMP content.

The results show that the myocardial cyclic AMP content in cyclosporine immunosuppressed cardiac transplant recipients is elevated compared with normal subjects. These levels are also quite elevated compared with measurements we have previously reported in other disease states including hypertrophic cardiomyopathy.[1] A cause and effect determination is not evident, but this observation provides further insight into potential biochemical and physiologic alterations that may account for functional abnormalities observed in the transplanted human heart. Chronic denervation of the heart leads to depletion of myocardial noradrenaline and changes in metabolism that include an increase in myocardial oxygen consumption.[5] Yellon had shown in isolated rat hearts that increases in myocardial cyclic AMP may be related to the extent and rate of contractile failure. Further evaluation and characterization of myocardial β-1 and β-2 receptor density/activity and adenylate cyclase activity and the complex interaction among cyclosporine, calmodulin and phosphodiesterase activity will be required. Regardless of the mechanism, the presence of elevated myocardial cyclic AMP suggests an underlying abnormality exists that may explain the pathogenesis of left ventricular hypertrophy and dysfunction that occurs after cardiac transplantation.

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Ventricular Tachycardia and Torsades de Pointes Complicating Pentamidine Therapy of Pneumocystis Carinii Pneumonia in the Acquired Immunodeficiency Syndrome

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Torsades de pointes is a polymorphic ventricular tachycardia (VT) that occurs in the setting of acquired or idiopathic QT-interval prolongation and may be facilitated by nutritional deficiency[1] and electrolyte abnormalities.[2] Four reports have associated the occurrence of this arrhythmia in patients with the acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia with QT-interval prolongation related to the use of pentamidine isethionate.[3-6] We have recently seen 4 patients who developed torsades de pointes or monomorphic VT during the course of pentamidine treatment for *P. carinii* pneumonia and a description of them follows.

The patients' clinical features, heart rate corrected QTc intervals immediately before administration of pen-

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tamidine therapy and at the time of the arrhythmic event, and serum electrolyte levels at the time of the event are listed in Table I. The first patient had an episode of syncope after 5 days of pentamidine therapy; on the tenth day of treatment she developed sustained polymorphic VT, which responded to thump cardioversion followed by lidocaine infusion and electrolyte repletion. The second patient developed polymorphic VT on the fourteenth day of pentamidine treatment that responded to direct-current shock, lidocaine infusion and electrolyte repletion. The third patient developed polymorphic VT on the ninth day of pentamidine therapy, which eventually responded to lidocaine infusion and multiple direct-current countershocks. The fourth patient developed frequent multifocal ventricular ectopic activity followed by a run of nonsustained VT on the twelfth day of pentamidine therapy. Magnesium was administered and pentamidine was discontinued. The patient's ectopy diminished and his QTc interval slowly returned to baseline. Pentamidine was restarted on the eighteenth hospital day and within 5 days the patient's QTc had again increased to 520 ms.

None of the 4 patients were receiving digoxin, diuretics or antiarrhythmic drugs before the arrhythmic event and none had any previous history of cardiac arrhythmia. All had tolerated intravenous pentamidine therapy during previous episodes of P. carinii *pneumonia, and all had been receiving aerosolized pentamidine before hospitalization. All patients were cachectic and all had important electrolyte abnormalities (hypomagnesemia or hypokalemia, or both) at the time of the arrhythmia.*

Hypomagnesemia and hypokalemia may each predispose to the development of torsades de pointes.[2] Although hypokalemia or hypomagnesemia have been found in other cases of torsades during pentamidine treatment of *P. carinii* pneumonia,[3,4] the arrhythmia has also been reported during pentamidine treatment when these electrolytes were normal.[5,6] Pentamidine itself may have independent adverse cardiac electrophysiologic effects. Wharton et al[3] observed that pentamidine is structurally similar to procainamide and might lead to QTc prolongation in some patients. A recent preliminary report has suggested that pentamidine-related QT prolongation occurs in only a small proportion of patients, but the combination of drug effect and electrolyte abnormalities may potentiate the electrophysiologic actions of either factor acting alone.

TABLE I Clinical, Electrocardiographic and Biochemical Features of Four Patients with Pentamidine-Associated Ventricular Tachycardia

			VT Episode			
Pt	Age (yrs)	Baseline QTc (ms)	Event	QTc (ms)	K^+ (mmol/liter) 3.5–5.1	Mg^{++} (mEq/liter) 1.5–1.9
1	30	481	TDP	562	3.3	0.6
2	37	433	TDP	638	2.4	0.9
3	37	392	TDP	503	3.6	1.2
4	38	422	NSVT	620	3.9	1.4

K^+ = potassium ion; Mg^{++} = magnesium ion; NSVT = nonsustained ventricular tachycardia; TDP = torsades de pointes; VT = ventricular tachycardia.

During pentamidine therapy a patient's nutritional status should be optimized. Potassium and magnesium levels should be followed closely and aggressively replaced. Patients receiving intravenous pentamidine should be monitored regularly by electrocardiography with careful attention to the QTc interval. Appreciable tissue levels of pentamidine may be present months after discontinuation of the drug[7] and a case of torsades de pointes has been reported in association with trimethoprim-sulfamethoxazole, the other first-line drug for the treatment of *P. carinii* pneumonia.[8] Patients who develop polymorphic or monomorphic VT during pentamidine treatment of *P. carinii* pneumonia may benefit from bolus magnesium sulfate injection[9] and, if the arrhythmia persists, rapid overdrive pacing or isoproterenol infusion. The role of type Ib agents is unresolved but all of our patients had favorable responses to lidocaine.

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CASE REPORTS

Thoracoabdominal Ectopia Cordis with Isolated Infundibular Atresia

Tal Geva, MD, Stella Van Praagh, MD, and Richard Van Praagh, MD

Ectopia cordis is a rare congenital anomaly in which the heart is partially or totally outside the thorax.[1] The thoracic and thoracoabdominal forms of ectopia cordis have been considered to constitute together 97% (138 of 142) of the cases.[2] The cervical form, found in 4 out of 142 cases, has been described only in malformed fetuses.[2] Complete abdominal ectopia cordis was thought previously to be represented only by Deschamp's case that was reported in 1806 by Cullerier.[3] However, whether or not complete abdominal ectopia cordis really exists and, if so, how it should be defined, remain unclear. We present a unique case of ectopia cordis that superficially resembles complete abdominal ectopia cordis. This patient has the following previously undescribed cardiac anomaly: isolated atresia of the subpulmonary infundibulum with an intact ventricular septum and a well-formed and patent pulmonary valve.

A 1,483 g white male infant was born at 34-weeks gestation to a 24-year-old, gravida 1, para 0 woman. At 32-weeks gestation, a fetal ultrasound study was performed for evaluation of polyhydramnios. A large ventral abdominal wall defect was shown with herniation of the heart and the abdominal viscera into the amniotic cavity. Two weeks later, the patient was born by vaginal delivery after premature onset of uterine contractions and rupture of the membranes. The patient died 5 hours after birth.

At autopsy, there was a large right paramedian gastroschisis extending from the right paraumbilical area inferiorly to immediately below the right costal margin superiorly (Figure 1). The liver, stomach, spleen, small bowel, large bowel and pancreas, herniated through the gastroschisis, with no remnant of peritoneal covering. The heart herniated through the cephalic portion of the gastroschisis (Figure 1). The sternum was intact except for absence of the xiphoid process. The pleural cavities were totally separated from the mediastinum by the confluence of the muscular components of the diaphragm laterally and the superior portion of the parietal pericardium medially (Figure 2). The central fibrous portion of the diaphragm was absent. The superior parietal pericardium arched up to the pericardial reflections of the great arteries and the superior vena cava. The pleural cavities were isolated from the mediastinal and the abdominal cavities by the superior parietal pericardium. The superior vena cava, main pulmonary artery, aorta and pulmonary veins passed through the superior parietal pericardium into the superior mediastinum (Figure 2). The lungs were hypoplastic, but normally lobed. Bilateral pleural effusions were present. The apex of the naked heart was cephalically oriented (Figure 1). The segmental organization of the heart was normal {S,D,S}[1] with normal alignments and connections. The subpulmonary infundibulum was atretic immediately below the pulmonary valve (Figure 2) with the ventricular septum being intact. The pulmonary valve anulus was hypoplastic but all 3 commissures were present and the valve was patent (Figure 2). The right ventricle was small-chambered and thick-walled with severe endocardial fibroelastosis. Additional findings included a patent foramen ovale, patent ductus arteriosus and bilateral atresia of the renal arteries. Chromosomal analysis was normal.

Did our case and Deschamp's case really have complete abdominal ectopia cordis? We think that the answer is no. In our case, the central tendon of the diaphragm, which is

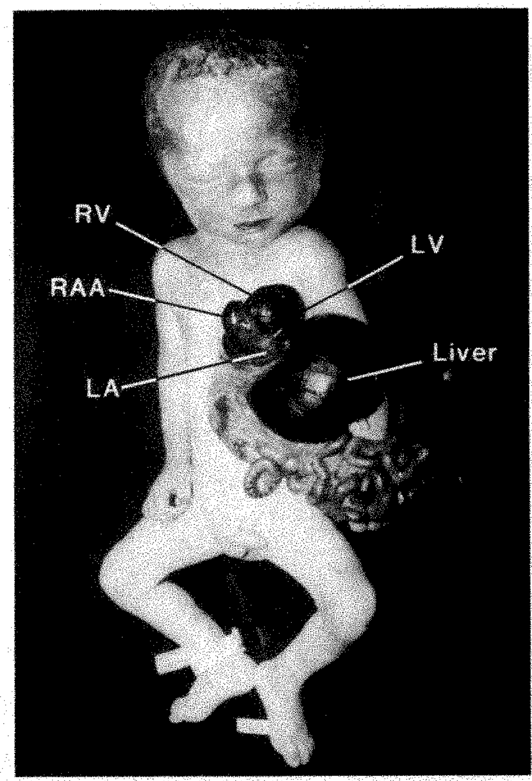

FIGURE 1. Thoracoabdominal ectopia cordis and gastroschisis. The cardiac apex points cephalically toward the left shoulder. LA = left atrium; LV = left ventricle; RAA = right atrial appendage; RV = right ventricle.

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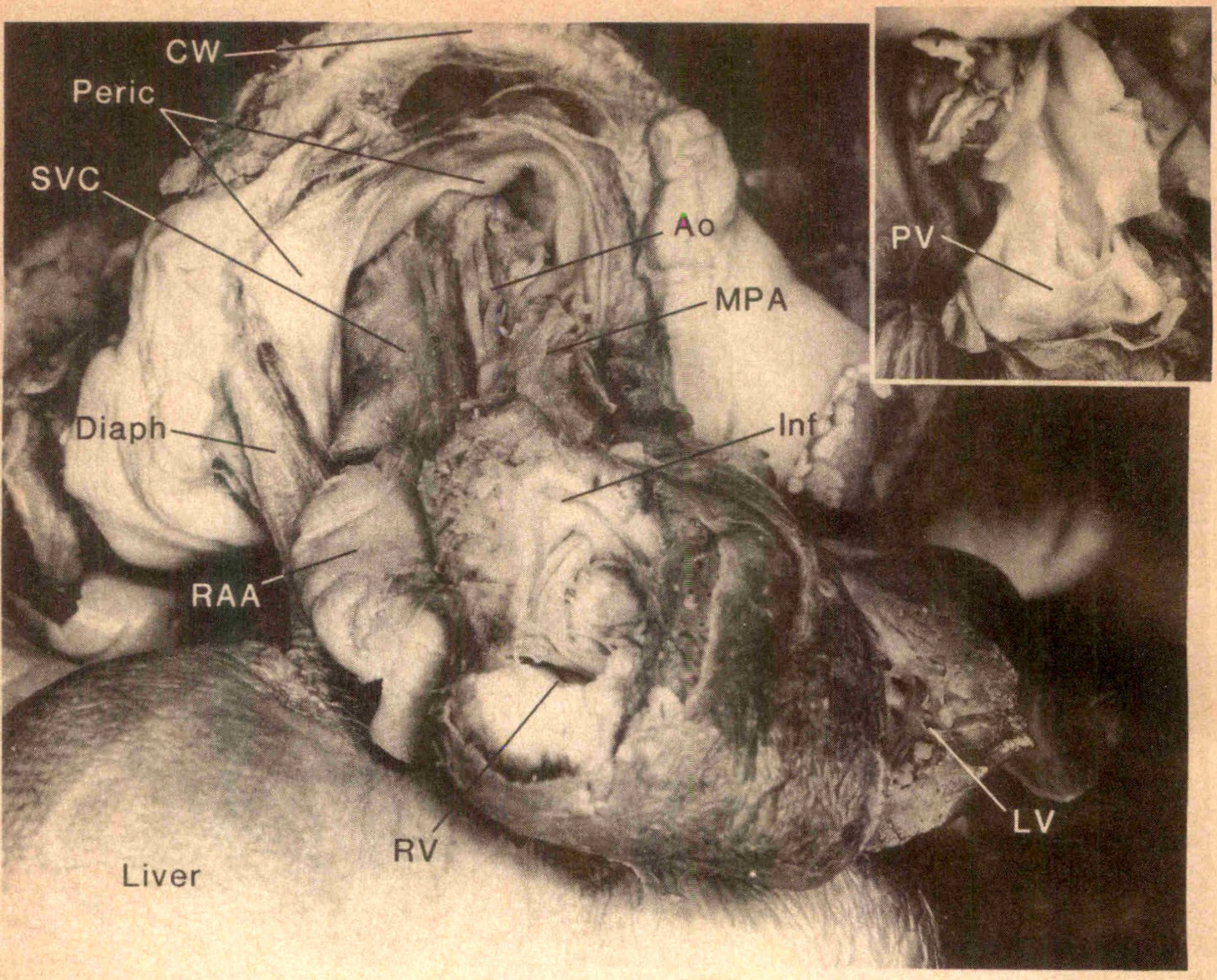

FIGURE 2. Frontal and inferior view of the heart and the thoracoabdominal communication. The thoracic and abdominal cavities are separated by the muscular diaphragm laterally (Diaph), which is confluent with the superior parietal pericardium, medially (Peric). The right ventricle is thick-walled and small-chambered with severe endocardial fibroelastosis. Note atresia of the subpulmonary infundibulum (Inf). ***Upper right corner,*** **opened main pulmonary artery showing patent pulmonary valve (PV). Ao = aorta; CW = chest wall; SVC = superior vena cava; other abbreviations as in Figure 1.**

derived from the septum transversum of the embryo,[4,5] was totally absent. Hence, a huge diaphragmatic defect was present. The confluence of the muscular leaves of the diaphragm laterally with the parietal pericardium medially, initially produced the erroneous impression that the diaphragm was intact. In fact, our case is an extreme form of the Cantrell syndrome[5] with free communication between the mediastinum and the abdominal cavity, that is, thoracoabdominal ectopia cordis. Our case is different from the classic Cantrell syndrome because the sternum was only minimally involved with absence of the xiphoid process. Gastroschisis is another unique feature of our case. Most previously reported cases of thoracoabdominal ectopia cordis have had either a ventral hernia or an omphalocele.[4]

Deschamp's case[1] was a previously healthy French soldier who died of pyelonephritis. At autopsy, the left kidney was absent and in its place was the heart within its pericardial sac. Although we previously considered this case to be the only documented example of complete abdominal ectopia cordis,[1] after careful reevaluation it became apparent that this was a case of inferior diaphragmatic eventration. The diaphragm was intact and markedly displaced inferiorly and the heart communicated only with the thoracic cavity. Hence, to the best of our knowledge, a genuine case of complete abdominal ectopia cordis has not been documented in which the heart is positioned below an intact diaphragm and is separated completely from the thoracic cavity. We strongly suspect that the abdominal form of ectopia cordis, defined strictly (as above), does not exist. We therefore propose that the abdominal form be deleted from the classification of ectopia cordis.[1]

The most common forms of congenital heart disease associated with ectopia cordis are tetralogy of Fallot and ventricular septal defect.[1] Rarely, ectopia cordis can occur with a structurally normal heart. Isolated atresia of the subpulmonary infundibulum with a patent and structurally normal pulmonary valve is documented here for the first time (Figure 2).

Could external compression produce atresia of the subpulmonary infundibulum? The human embryo is flexed ventrally during the first 3 weeks after ovulation. At approximately 23 days of gestation, the developing heart descends from the neck into the thorax, which is still widely patent (complete thoracic ectopia cordis and omphalocele normal at this stage).[1] During the subsequent 11 to 15 days (until 34 to 36 days of gestation), the rapidly developing embryonic head is ventrally flexed, resulting in cephalocardiac approximation.[1] Normally, at about 37 to 38 days of gestation, the embryo starts to straighten out and the heart fits into the developing chest. The semilunar valves and the truncal septum complete their development during Streeter's horizon XVII, that is, 34 to 36 days of gestation. Approximately during that period, the medial migration and fusion of the paramedian mesenchymal somites normally results in the formation of an intact thoracic and abdominal ventral wall.[4,6] The aforementioned embryologic observations suggest the hypothesis that failure of abdominal wall fusion, associated with a defect in or absence of septum transversum, may allow herniation of the heart into the amniotic cavity through these defects. Extrinsic compression of the ectopic and "unprotected" heart may result in the unique anomaly displayed by our patient, isolated infundibular atresia.

Another form of mechanical teratogenesis by amniotic band(s) was described by Kaplan et al.[6] Because there was no evidence of amniotic sac rupture with amniotic band formation in our case, absence of the septum transversum component of the diaphragm and failure of fusion of diaphragm and failure of fusion of the abdominal wall appear to be the main morphogenetic mechanisms leading to extreme thoracoabdominal ectopia cordis in our patient.

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Primary Sarcoma of the Heart Causing Mitral Stenosis

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Cardiac sarcomas are rare and mitral stenosis caused by this neoplasm in the left atrium is even rarer. Such was the case, however, in the patient to be described herein.

A 46-year-old woman (CC no. 22-72-58-1) who died on January 7, 1990, had been well until April 1989, when she had an episode of dizziness and right eye blindness that resolved spontaneously. In June 1989, she had a transient episode of right lower arm numbness and right eye blindness that resolved spontaneously. In September 1989, she developed orthopnea, dyspnea with walking, syncope and easy fatigability. In October 1989, examination by a cardiologist disclosed a loud first heart sound, a grade 1/6 systolic ejection murmur at the left sternal border and apex that radiated into the axilla and a grade 2/6 systolic murmur at the right sternal border that increased with inspiration. Chest radiograph suggested a dilated left atrium and was consistent with congestive heart failure. An echocardiogram disclosed severe mitral stenosis, mild mitral regurgitation, a dilated right atrium and right ventricle, pericardial effusion and a large mass in the region of the posterior mitral leaflet protruding into and obstructing the mitral orifice (Figure 1). Cardiac catheterization revealed the following pressures (in mm Hg): right atrial mean, 20; right ventricular, 105/18; pulmonary artery wedge mean, 35; left ventricular, 125/18; and aortic, 125/80. The pulmonary artery wedge—left ventricular mean diastolic gradient was 20 mm Hg. The left ventricle contracted normally. By angiography, neither mitral nor aortic valve regurgitation was present and the epicardial coronary arteries were normal. Thoracotomy was performed and a "lemon"-sized mass involving the basal portion of the left ventricular wall was found. Computed tomography after operation localized the mass to the region of the posterior mitral leaflet. Electrocardiogram showed changes of right ventricular hypertrophy, incomplete right bundle branch block and left atrial abnormality. Echocardiogram showed a large mass in the region of the mitral valve and it extended into the left atrium and left ventricle. By Doppler, the estimated mean mitral pressure gradient was 18 mm Hg. Magnetic resonance imaging (Figure 2) confirmed these findings. The patient received radiation therapy, but died suddenly.

At necropsy (A90-2), the heart with the neoplasm weighed 530 g. The visceral and parietal pericardia

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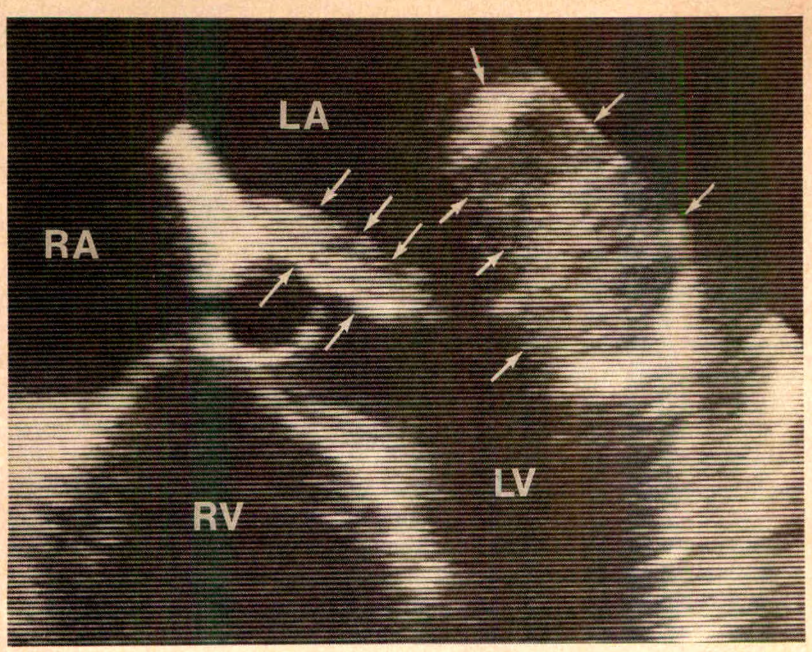

FIGURE 1. Transesophageal echocardiogram showing the tumors *(arrows)* in the left atrial (LA) wall. LV = left ventricle; RA = right atrium; RV = right ventricle.

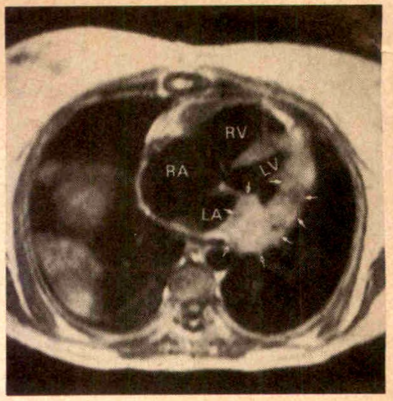

FIGURE 2. Magnetic resonance image of thorax showing the tumor in the walls of left atrium (LA) and left ventricle (LV) and pulmonary infarcts in 1 lung from occlusion of several pulmonary arteries by sarcoma from the right atrium. Abbreviations as in Figure 1.

were adhered to one another by fibrous and neoplastic adhesions. The neoplasm in the wall of the left atrium caused severe obstruction to the mitral orifice (*Figure 3*) *and also to the left pulmonary veins. The neoplasm also invaded the coronary sinus, basal portion of the left ventricular wall and a single tumor deposit was present in the right atrial cavity at the orifice of the coronary sinus. The only body organ containing the neoplasm other than the heart was the lung; a tumor was present in several pulmonary arteries with resulting pulmonary infarcts. Histologically, the neoplasm was a spindle-cell sarcoma. Both pleural spaces* (*approximately 1,000 ml each*) *and the peritoneal cavity* (*1,400 ml*) *contained dark, amber-colored watery fluid.*

The aforementioned patient had sarcoma involving the left atrium and the tumor extended into the mitral orifice producing severe mitral stenosis. We found 7 previously reported cases of left atrial sarcoma causing mitral stenosis and pertinent observations in them are listed in Table I.[1-7] Only 1 of the previously reported cases had the mitral obstruction confirmed by catheterization,

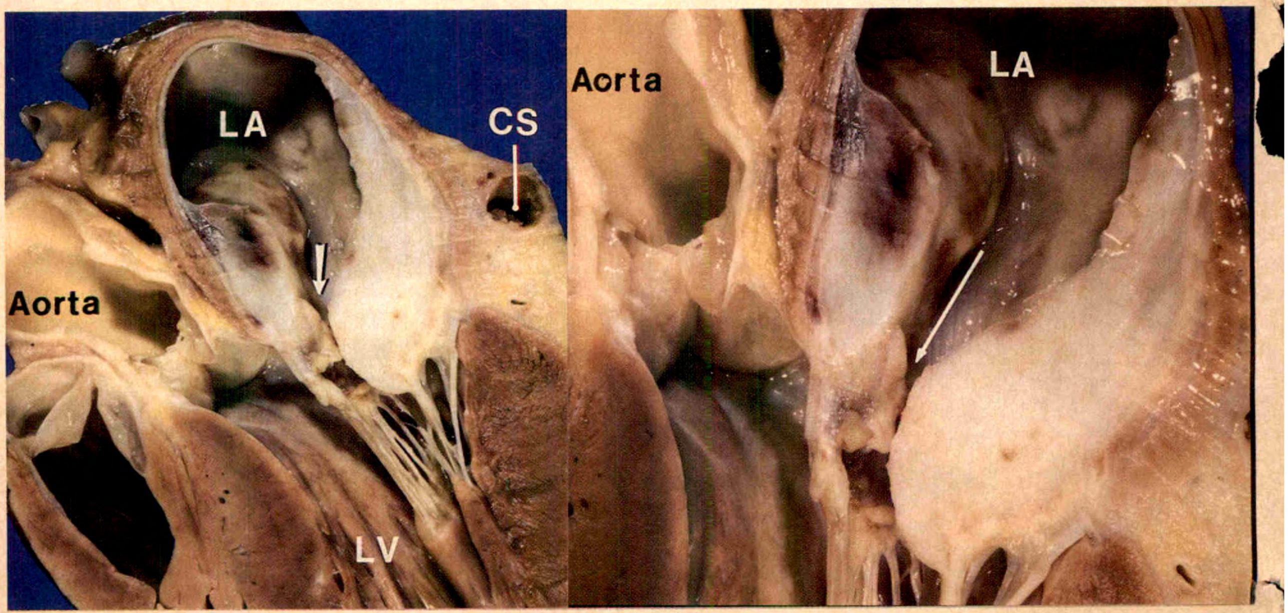

FIGURE 3. Photographs of longitudinal views of the heart showing large tumor deposits in the wall of left atrium (LA) with resulting severe obstruction *(arrows)* to the mitral valve orifice. Tumor also invaded the coronary sinus (CS). Abbreviations as in Figure 1.

TABLE I Observations in Previously Reported Patients with Left Atrial Sarcoma Causing Mitral Stenosis

Case	First Author	Year	Age (yr) & Sex	Duration of Symptoms (months)	DM	OS	P_2	PAW-LV MDG (mm Hg)	Echocardiographic Evidence of MS	Type of Sarcoma
1	Muir	1966	50 F	3	0	—	—	—	—	Chondrosarcoma
2	Dutschmann	1974	39 F	7	+ (4/6)	+	+	—	—	Rhabdomyosarcoma
3	Shuh	1978	37* F		+ (2/6)	+	+	—	—	Fibrous histiocytoma
4	Frendsen	1981	39 F	0.5	+	—	—	—	—	Mesenchymoma
5	Terashima	1983	27 F	5	—	—	—	—	—	Fibrous histiocytoma
6	Ormerod	1984	48 M	"Weeks"	+	—	—	—	+	Angiosarcoma
7	Villasenor	1985	82 F		+ (2/6)	+	—	28	+	Rhabdomyosarcoma

* Only patient still alive at follow-up.

DM = diastolic murmur; LV = left ventricle; MDG = mean diastolic gradient; MS = mitral stenosis; OS = opening snap; PAW = pulmonary arterial wedge; P_2 = pulmonary component of second heart sound; † = increased; + = present; 0 = negative; — = no informatiion.

but all had clear anatomic evidence of mitral obstruction by the neoplasm. Another unusual feature of this sarcoma was invasion of the coronary sinus by the neoplasm and migration (embolization) of the neoplasm from the lumen of the coronary sinus into the right atrium. Portions of the right atrial tumor migrated into several peripheral pulmonary arteries (another embolism), causing neoplastic pulmonary infarcts.

1. Muir CS, Seah CS. Primary chondrosarcomatous mesenchymoma of the mitral valve. *Thorax 1966;21:254–262.*

2. Dutschmann L, Duarte S, Da Costa JN. Rhabdomyosarcoma of the heart (a case of unusual localization). *Angiology 1974;25:186–196.*

3. Shah AA, Churg A, Sbarbarao JA, Shepard JM, Lamberti J. Malignant fibrous histiocytoma of the heart presenting atrial myxoma. *Cancer 1978;42:2466–2471.*

4. Frandsen NE, Andersen G, Nielsen JR. Malignant mesenchymoma of the heart presenting as mitral stenosis. *Acta Med Scand 1981;209:235–237.*

5. Terashima T, Aoyama K, Nihei K, Nito T, Imai Y, Takahashi K, Shichibei D. Malignant fibrous histiocytoma of the heart. *Cancer 1983;52:1919–1926.*

6. Omerod OJ, Spratt PM, Lewis NP, Wallwork J. Primary angiosarcoma of the heart mimicking a left atrial myxoma. *Thorax 1984;39:798–799.*

7. Villasenor HR, Fuentes F, Walker WE. Left atrial rhabdomyosarcoma mimicking mitral valve stenosis. *Tex Heart Inst J 1985;12:107–110.*

FROM THE EDITOR

We Think We Are One, We Act As If We Are One, But We Are Not One

Natural carnivores live on meat. Natural herbivores live on vegetables, fruits and starches (rice, corn, potatoes, beans, pasta). Carnivores and herbivores are made differently (Table I). Carnivores have claws and sharp teeth for ripping meat apart; herbivores have hands (unless they have hoofs) for gathering food and flat teeth for grinding the vegetables, fruits and grains. Carnivores have short bowels and rapidly digest the flesh and rapidly excrete the putrefying animal products. The time required for food to travel through their intestinal tract is short. Herbivores have long intestines so that there is plenty of time to digest the nutrients in the plants, fruits and starches, and when these animals eat these foods their transient times also are relatively short despite the long intestinal tracts. Meat eaters pant to cool themselves and lap water; plant eaters, in contrast, sweat to cool and sip water. Carnivores synthesize their own vitamin C, which is virtually absent in meat and dairy products; herbivores obtain their vitamin C from plant foods in which it is abundant.

Although human beings eat meat we are not natural carnivores (Table I). We were intended to eat plants, fruits and starches! No matter how much fat carnivores eat, they do not develop atherosclerosis. It is virtually impossible, for example, to produce atherosclerosis in the dog even when 100 grams of cholesterol and 120 grams of butter fat are added to its meat ration.[1] (This amount of cholesterol is approximately 200 times the average amount that human beings in the USA eat each day!) In contrast, herbivores rapidly develop atherosclerosis if they are fed foods, namely fat and cholesterol, intended for natural carnivores. Adding only 2 grams of cholesterol daily for 2 months to a rabbit's chow, for example, produces striking fatty changes in its arteries.[1] And humans are like rabbits, natural herbivores, not like dogs or cats, natural carnivores.

TABLE I Differences in Carnivores and Herbivores

Characteristic	Carnivores	Herbivores
Appendages	Claws	Hands or hoofs
Teeth	Sharp	Flat
Intestines	Short	Long
Body cooling	Pant	Sweat
Drinking water	Lap it	Sip it
Vitamin C	Make it themselves	Obtained solely from diet

Thus, although we think we are one and we act as if we are one, human beings are not natural carnivores. When we kill animals to eat them, they end up killing us because their flesh, which contains cholesterol and saturated fat, was never intended for human beings, who are natural herbivores.

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

1. Collens WS. Atherosclerotic disease: an anthropologic theory. *Medical Counterpoint.* December 1969;1:53–57.

Lopressor®

metoprolol tartrate USP

Tablets
Ampuls

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension

Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction

Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction

Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

> ***Ischemic Heart Disease:*** Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a $beta_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General

Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A $beta_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.
Please consult Brief Summary of Prescribing Information on following page.